Interactions of inhalational anesthetics and carbon dioxide absorbents

Keijzer, C.

2007

document version
Publisher's PDF, also known as Version of record

Interactions of inhalational anesthetics and carbon dioxide absorbents

Measurements of carbon monoxide and compound A in an anesthetic circuit

Christiaan Keijzer

Interactions of inhalational anesthetics and carbon dioxide absorbents. Measurements of carbon monoxide and compound A in an anesthetic circuit.

C. Keijzer, Dissertation, Vrije Universiteit Amsterdam

ISBN/EAN: 978-90-9022049-9

This dissertation was printed by Universal Press, Veenendaal, the Netherlands.

VRIJE UNIVERSITEIT

Interactions of inhalational anesthetics and carbon dioxide absorbents

Measurements of carbon monoxide and compound A in an anesthetic circuit

ACADEMISCH PROEFSCHRIFT

ter verkrijging van de graad Doctor aan
de Vrije Universiteit Amsterdam,
op gezag van de rector magnificus
prof.dr. L.M.Bouter,
in het openbaar te verdedigen
ten overstaan van de promotiecommissie
van de faculteit der Geneeskunde
op maandag 19 november 2007 om 13.45 uur
in de aula van de universiteit,
De Boelelaan 1105

door

Christiaan Keijzer

geboren te Zutphen

promotor: prof.dr. J.J. de Lange
copromotor: dr. R.S.G.M. Perez

De liefde is lankmoedig en goedertieren; de liefde is niet afgunstig, zij praalt niet, zij beeldt zich niets in.

Zij geeft niet om de schone schijn, zij zoekt zichzelf niet, zij laat zich niet kwaad maken en rekent het kwade niet aan.

Zij verheugt zich niet over onrecht, maar vindt haar vreugde in de waarheid.

Alles verdraagt zij, alles gelooft zij, alles hoopt zij, alles duldt zij.

De liefde vergaat nimmer. De gave der profetie zal verdwijnen, tongen zullen verstommen, de kennis zal een einde nemen.

1 Korintiërs 13,4-8

Contents

Chapter 1

General introduction :

Interactions of inhalational anesthetics and carbon dioxide absorbents

---

Christiaan Keijzer, Jaap J. de Lange, Roberto S.G.M. Perez

Introduction

Anesthesia is induced and maintained in patients to perform surgical procedures. Inhalational anesthetics are widely used for this purpose. To minimize the costs of use of inhalational anesthetics and medical gases like oxygen, patients are connected to an anesthesia circle machine to allow rebreathing of expired gases. An essential part of these anesthesia circle machines is the canister with carbon dioxide absorbent to prevent carbon dioxide intoxication in the patient. These absorbents contain calcium hydroxide to bind carbon dioxide, but also strong bases like potassium hydroxide and sodium hydroxide to facilitate this binding reaction. These strong bases are highly reactive, and already in 1979[1] it was demonstrated that halothane reacts with sodalime in anesthesia circle circuits, therewith generating volatile toxic degradation products. In recent years, results were published about carbon monoxide production from volatile anesthetics as a result of interaction with carbon dioxide absorbents. With the introduction of sevoflurane, reports quickly followed in which concerns were expressed regarding the nephrotoxic degradation product compound A, as a consequence of the interaction with carbon dioxide absorbents. The purpose of this general introduction is to present the history and recent findings of the interactions between inhalational anesthetics and carbon dioxide absorbents and to outline the aim of this thesis.

History of inhalational anesthetics

Nitrous oxide gas was discovered by Jean Baptiste van Helmont[2] (1579-1644) and first synthesized by Joseph Priestley[3] in 1772. Probably due to the impurities of this synthesized nitrous oxide, Priestly did not discover the anesthetic properties of this vapor, and it was later used for the social amusement and euphoria it produced. The analgesic effects of nitrous oxide were only discovered in 1844 when the dentist Dr. Horace Wells[4] tested nitrous oxide on himself and several patients performing tooth extractions.

Ether was discovered by a Spanish alchemist named Raymundus Lullius[5] in the thirteenth century and named it "sweet vitriol". Paracelsus[6] first distilled ether in the fifteenth century, rediscovering "sweet vitriol" for his own use. Remarkably, it lasted until 1842 until Dr. Crawford Long[7] used ether in three minor surgical procedures. He published his results only in 1849 thereby overtaken by the dentist W.T.G. Morton[8], who publicly demonstrated in 1846 the anesthetic effects of ether in a surgical removal procedure of a submandibular tumor.

In the fall of 1831, in almost the same month, three authors published their findings of the discovery of chloroform. These authors were Samuel Guthrie[9] in the United States, Eugène Soubeiran[10] in France and Justus von Liebig[11] in Germany. Chloroform was introduced as an anesthetic, by Dr. J.Y. Simpson[12] in 1847.

After Morton a new era for surgery was born. Other agents than these were not considered until 1920-1940 when ethylene, cyclopropane and divinyl ether were discovered and won acceptance due to rapid recovery from anesthesia. With the exception of nitrous oxide all these agents were replaced by the modern inhaled anesthetics. The modern agents differed from previous halogenated compounds in the substitution of fluorine for chlorine (or heavier halogens). Fluorine provided greater molecular stability and lower solubility. The first of the modern inhaled anesthetics was fluroxene, followed by halothane (a derivative from chloroform) and methoxyflurane, enflurane, isoflurane, sevoflurane and desflurane (all derivatives from diethyl-ether). Commonly used today are isoflurane, sevoflurane and desflurane. Halothane and enflurane are no longer commercially available on the European market.

History of CO_2 absorption

Anesthesiologists at the first half of the 20th century had to bring their own equipment and anesthetic agents to the institutions where they practiced. Therefore it was necessary to develop systems to reuse the expired anesthetics from the patient from an economical point of view. For

rebreathing of expired gasses it is necessary to absorb the carbon dioxide because of the toxic effects of high dosages of carbon dioxide when rebreathed.

In 1755 Joseph Black[13] described the relationship between carbon dioxide and the hydroxides of sodium and calcium. Alfred Coleman[14] developed a system of carbon dioxide absorption by passing the expired gases over slaked quick lime in 1869. In 1898, Benedict and Tower[15] defined a method for the preparation of granular and hydrated soda-lime with a higher carbon dioxide absorbent capacity. Dennis Jackson[16] demonstrated in 1915 the practical use of soda lime absorption by maintaining stable levels of anesthesia in animals while using minimal amounts of ether. His idea was adapted by Ralph Waters[17] in 1923 by attaching a canister with granular sodalime to a breathing hose close to the face, while the expired gases were lead to a rebreathing bag. In this rebreathing bag, fresh oxygen and/or nitrous oxide was added. This device was altered in 1930 by Brian C. Sword[18] by creating two hoses to the airway, one for inspired and one for expired gases. From here on the circle breathing system was developed with an integrated ventilator, which is still the most popular breathing system/anesthesia machine used today.

Carbon monoxide

Carbon monoxide is a clear, odorless, tasteless, and non irritating gas mostly produced as a result of incomplete combustion of organic materials. Average CO concentration in the atmosphere is 0.1 ppm (parts per million) but in cities with much traffic it can reach up to 115 ppm. The Environmental Protection Agency standards for CO are 9 ppm for an 8-hour exposure and 35 ppm for an 1-hour exposure. Next to traffic, smoking is another important source of carbon monoxide, which can cause an increase of carboxyhemoglobin (COHb) levels up to five times. Carbon monoxide is also produced in the human body[19] as a result of hemoglobin metabolism. In the normal adult, 4 grams of hemoglobin is broken down every day resulting in 6.8 mg CO. When inhaled carbon monoxide binds to hemoglobin on the oxygen binding site to form COHb, it can no longer bind oxygen.

Hemoglobin's affinity for carbon monoxide is 220 times that of oxygen which can lead to hypoxia if CO concentrations are sufficiently high. Exposure of 500 ppm CO results in a COHb level of 20% and 1000 ppm at a level of 50%. Toxicity of carbon monoxide becomes worse as a result of a shift of the oxygen-hemoglobin dissociation curve to the left which leads to a higher affinity of hemoglobin for oxygen, therefore resulting in an impaired oxygen extraction from the hemoglobin molecule at tissue level. Toxicity of CO as function of exposure is defined in the Henderson and Haggard's Index of Toxic Effect[20]:

CO concentration (ppm) x Time (hours) = Index of Toxic Effect

300 - no perceptible effect

600 - barely perceptible effect

900 - nausea and headache

1500 - dangerous to life

CO is oxidized to carbon dioxide[21] but this oxidation rate is insignificant when compared to the production rate of CO as a result of hemoglobin break down.

In the awake patient the first symptoms of CO poisoning with COHb levels of 10-20% are: complaints of headache and tightness across the forehead and a "cherry-red" colour of the skin particularly in the face. With increasing COHb levels of 30-50% the heart rate will increase to compensate for hypoxic peripheral vasodilation and the lactic acidosis resulting from tissue hypoxia. When COHb levels reach 40-60% the respiratory rate increases, although the partial oxygen pressure is not reduced and so there is no carotid and aortic chemoreceptor stimulation. After COHb concentrations reach 60% cardiovascular collapse, respiratory failure and death will follow.

In an anaesthetized patient, these signs and symptoms will not be evident until a very severe state. Standard dual-wavelength pulse oximeters cannot differentiate between O_2Hb and COHb. Even at COHb concentrations of 70%, the pulse oximeter still reports a SpO_2 of 90%[22]. The technique of multiple wavelength oximetry that can differentiate between O_2Hb and COHb is already available for some time[23] but only just recently the first commercially available multiple wavelength pulse oximeter came available[24].

From mass spectrometers it is also known that it will not measure carbon monoxide in an anesthetic circuit correctly, because of the molecular weight of CO and nitrogen are the same.

Another problem of carbon monoxide in an anaesthetized patient is that in a closed circle circuit[25;26], the normally exhaled endogenous produced gasses like carbon monoxide, methane, acetone and nitrogen are also reused and inhaled again, and therefore accumulate in the anesthesia circuit when a low fresh gas flow is used (< 1 litre/min).

Carbon monoxide as reaction product of inhalational anesthetics with carbon dioxide absorbents

In 1990 Moon et al.[27] was the first to present a report of three patients with elevated COHb levels between 11 and 29 % during enflurane anesthesia with a fresh gas flow (FGF) of more than 2 litre/minute. These patients were the first to be operated on a Monday morning, suggesting that a chemical reaction had occurred in the anesthesia circuit or absorbent during the weekend. A sample from the anesthesia circuit revealed a carbon monoxide concentration of 240 ppm. This report was followed by an abstract in 1991 from the same author[28] who reported about CO concentrations in absorbent canisters after several days of use. Measurements were performed with a CO analyzer and confirmed with an infrared analyzer. One canister contained more than 1000 ppm CO. Moon also found traces of formate in used sodasorb canisters, which, as Moon suggested, might be a possible intermediate in carbon monoxide production.

In vitro and animal studies

After the publications of Moon et al., discussions[29-32] about this subject appeared in literature, and in 1995 Fang et al.[33] published an extensive in vitro study for all modern inhaled anaesthetics in combination with soda lime or Baralyme®, containing different percentages of water from dry to fresh absorbents at different temperatures. The main conclusions: the magnitude of CO production is desflurane ≥ enflurane > isoflurane >> halothane = sevoflurane. No data were published about halothane and sevoflurane, except for a remark that only very little CO was produced at high temperature with completely dry absorbent, and therefore not clinically relevant. No carbon monoxide was produced with soda lime containing 4.8% water or more and Baralyme® with 9.8% water or more. Highest levels of CO were produced with completely dry absorbents, and more in Baralyme® than soda lime at equal water percentages. Higher temperature of absorbents increased CO production.

Frink et al.[34] followed with a report of high COHb levels in pigs after exposure to desflurane anesthesia with Baralyme® which was dried with 2, 6 or 10 litre/min oxygen flow during 48 hours. Highest levels of COHb were found in the group with the highest oxygen flow over the absorbent prior to anesthesia, a probe of the Baralyme® revealed a water content less then 5,5%. The publication of Frink et al.[35] demonstrated peak concentrations of 37,000 ppm carbon monoxide with Baralyme® exposed to 48 hours of a flow of 10 l/min of oxygen in combination with 7,5 vol% desfllurane. The measured water content of Baralyme® was 1.2 to 3.9 %. Drying of Baralyme® or sodalime during 24 hours revealed water contents of respectively 1.9 to 4.8 % and 3.8 – 6.7 %.

Bonome et al.[36] published an abstract with CO concentrations in an in vitro situation using an anesthesia machine containing soda lime with a hydration level of 1 and 2,5%. To obtain CO production 3,5 and 7% desflurane and 1,5% isoflurane was used. The highest carbon monoxide concentration was 4130 ppm with 7% desflurane in soda lime with a 1% water content. For isoflurane this was 2200 ppm. In another abstract[37], the drying time of sodalime was measured. A

FGF of 7 l/min of oxygen during 41 hours was sufficient to desiccate a standard anesthesia machine container with sodalime. In a later published study[38] the authors demonstrated that higher volatile anesthestic concentrations and a lower fresh gas flow increased the amount of carbon monoxide produced.

From these in vitro studies we conclude that there is a potential risk of carbon monoxide production when a carbon dioxide absorbents becomes desiccated. Sufficient drying time with a high gas flow of oxygen is needed, but this could occur for example on a Monday morning when the anesthesia machine with an open oxygen flow regulator is not turned off on the previous Friday.

In vivo studies

Baum et al.[39] presented an in vivo study in which COHb was measured half an hour after induction of anesthesia, maintained with isoflurane or enflurane in a low flow circle circuit with previeously used soda lime as absorbent in the anesthesia circuit. No dangerously high COHb levels were found. The only significant difference in COHb concentrations was found between smokers and nonsmokers.

Harrison et al.[40] presented similar conclusions with an in vitro and in vivo study in an anesthesia circuit with unventilated fresh and used soda lime, and fresh and used soda lime that were ventilated with 2 l/min oxygen during 15 hours. Halothane, isoflurane and enflurane were used as anaesthetics. CO was measured with a Bedfont Mini Smokerlyzer EC50. In vitro CO levels were below 1 ppm. In vivo, no CO was found in the inspiratory branch of the circuit and low CO levels in the expiratory branch, with a significant difference between smokers and nonsmokers. Their conclusion was that only carbon monoxide from the patient was measured and none from the anesthesia circuit.

Hendrickx et al.[41] presented a similar study as Baum's, but compared COHb before and after the operation, whereby isoflurane or desflurane was used for maintaining anesthesia. No COHb increase was found after 1 hour of low flow anesthesia, nor after 2 hours.

We can conclude from these in vivo studies that desiccation of the carbon dioxide absorbent in clinical practice is a rare phenomenon. Not without risk, however, as demonstrated by the previously mentioned in vitro studies and a case report published by Berry et al.[42]. Here, a 24-yr-old woman was anesthetized for a clinical research study including the use of 5% desflurane. Because of a SpO_2 decrease to 93% five minutes after induction while the patient was ventilated with 100% oxygen bilateral auscultatation of the lungs revealed no abnormalities. Ten minutes after induction of anesthesia, the gas analyzer reported that enflurane was present besides desflurane. At this point carbon monoxide toxicity was suspected, and the absorbent (Baralyme®) was replaced after 15 minutes of anesthesia. An arterial blood gas sample revealed a carboxyhemoglobin level of 36%. The patient recovered uneventfully from this intoxication. Subsequent inquiries revealed that the anesthetic machine had not been used for several days and had probably been left switched on with an oxygen flow present for the entire period.

Possible mechanisms of action of carbon monoxide production and desiccated carbon dioxide absorbents.

In 1995 Abbott International presented a carbon monoxide positioning paper as a direct result of a review by an opinion leader. The consensus presented in this paper was that there was no basis for support of a potential interaction between sevoflurane and CO_2 absorbents to produce CO. A potential mechanism of carbon monoxide production was presented (figure 1.1), which suggested

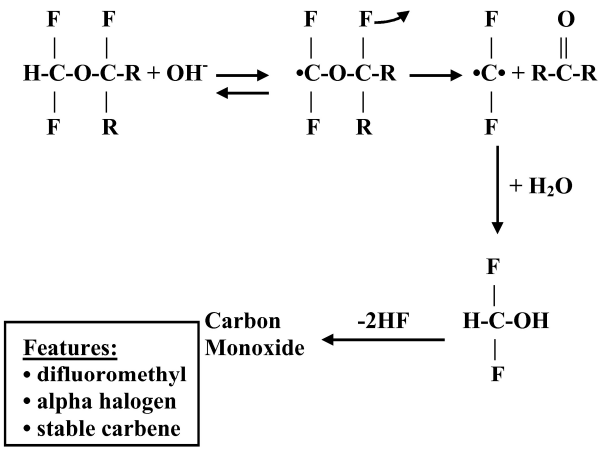


Figure 1.1 Potential mechanism of carbon monoxide production from anesthetics.

that a reaction between enflurane, desflurane or isoflurane with a strong base may form an unstable intermediate, whereby a carbene is generated in the presence of a suitable leaving group on the alpha or beta carbon. The fluorine atoms render this stable carbene, which can subsequently react with water to liberate carbon monoxide. Formation of the carbene intermediate is only possible in the mentioned anesthetics because of the lack of the necessary difluoromethyl ($-CF_2H$) moiety in sevoflurane and halothane, as shown in figure 1.2.

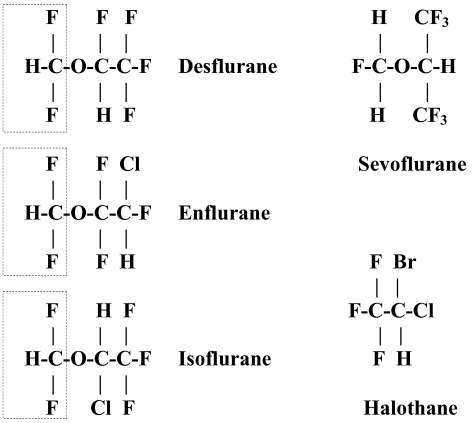


Figure 1.2 Carbon monoxide formation: structural correlations**.**

Baxter et al.[43] demonstrated the feasibility of this theory by measuring carbon monoxide formation from desiccated barium hydroxide lime or sodalime from deuterium-substituted anesthetics. The

proton abstraction from the anesthetics by a strong base was determined by deuterium isotope exchange and the source of the oxygen was identified by ^{18}O incorporation in the absorbent. This proton abstraction from the anesthetics was dependent on the lack of water and was greater with potassium than sodium hydroxide. The latter explains the higher CO production of Baralyme® than sodalime, because of the higher potassium hydroxide content of Baralyme®. The oxygen in the produced CO seemed to originate from the absorbent. The authors then proposed a more detailed mechanism as shown in figure 1.3.

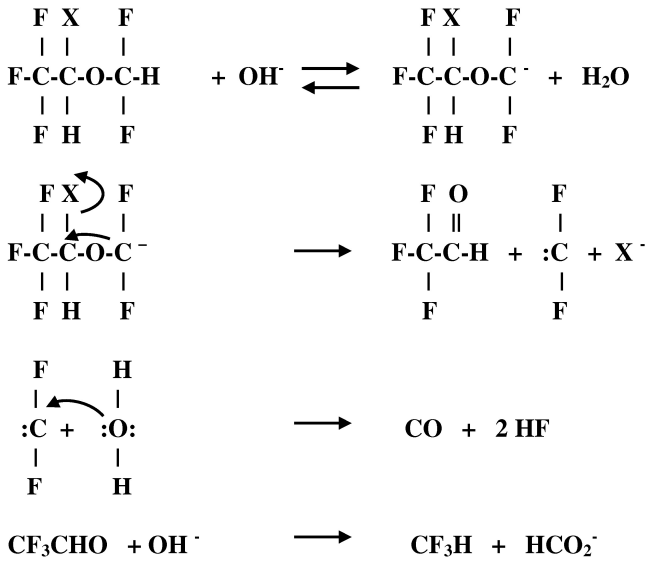


Figure 1.3 Proposed mechanism of carbon monoxide formation from difluoromethyl-ethyl ether anesthetics. Shown is the backbone structure for isoflurane (X = Cl) and desflurane (X = F). Also shown is a putative mechanism for the concomitant formation of trifuoromethane. Water in line 3 may also react as OH^-.
The difluoromethyl ethers desflurane, enflurane, and isoflurane undergo rapidly reversible base-catalyzed difluoromethyl proton abstraction to yield a difluoromethyl ethyl ether carbanion. This carbanion, in the presence of sufficient water, would simply reprotonate to regenerate the original anesthetic. In the absence of sufficient water, the carbanion could eliminate a halogen anion from the ethyl moiety α to the oxygen and decompose to difluorocarbene and the corresponding aldehyde. The difluorocarbene can subsequently react with hydroxide and/or residual water# in the absorbent to form CO, via difluoromethanol and formyl fluoride intermediates. Difluorocarbene could also react with CO_2 or silica in the absorbent to form CO. Formate may arise from formyl fluoride reaction with water or by subsequent reactions of CO. For desflurane and isoflurane, fluoride and chloride elimination, respectively, from the α-ethyl carbon would yield trifluoroacetaldehyde. Trifluoroacetaldehyde, in the presence of strong base, may further decompose to formate and trifluoromethane. **Figure and text reprinted with permission from Lippincot Williams & Wilkins: Baxter PJ et al.: Mechanistic aspects of carbon monoxide formation from volatile anesthetics. Anesthesiology 1998;89:929-941**

While this proposed mechanism states that carbon monoxide can only be produced from desflurane, enflurane and isoflurane, there are also reports of production of relative small amounts of CO from halothane and sevoflurane[44;45] that cannot be explained by this mechanism.

Changing the chemical composition of the carbon dioxide absorbent

The study by Baxter et al.[43] demonstrated that carbon monoxide production is dependent on the presence of strong bases like sodium hydroxide (NaOH) and potassium hydroxide (KOH). Neumann et al.[46] tested this theory by producing calcium hydroxide absorbents with different concentrations of these strong bases in desiccated and hydrated condition. The authors confirmed the theory that these strong bases are largely responsible for carbon monoxide production in desiccated absorbents. In 1999 the first strong base free absorbent was introduced: Amsorb® demonstrated a lack of carbon monoxide production capability in hydrated or desiccated conditions in vitro[47;48]. An in vivo study in pigs confirmed these findings[49]. Other absorbents with lower concentrations of strong bases or absorbents without strong bases soon became available, some of them were tested in desiccated condition in an in vitro study by Knolle et al.[50] using glass cylinders. This study also confirmed that lower concentrations of strong bases resulted in lower carbon monoxide production. Another carbon dioxide absorbent, lithiumhydroxide was tested by Stabernack et al.[48]. It demonstrated production of insignificant concentrations of carbon monoxide. Lithiumhydroxide is readily available, but not easy to handle because of the highly corrosive effect, and therefore not yet used in anesthetic machines. It is used in filled disposable absorbent containers in aerospace because of it's high carbon dioxide absorbing capacity.

Detection of carbon monoxide inside the anesthetic circuit.

Because of the risk of production of high concentrations of carbon monoxide when using desflurane and a desiccated strong base containing absorbent, one would like to detect carbon monoxide inside the anesthetic circuit. Although Woehlck et al.[51;52] published two papers in which he observed the mass spectrometer report traces of enflurane during isoflurane anesthesia with increasing COHb levels in the patient, the main problem at this moment is that there is no accurate in-line measurement of carbon monoxide available. The cause of enflurane detection during isoflurane

anesthesia seemed to be a trifluoromethyl cation, a degradation product of isoflurane and enflurane, which, when produced, might be an indicator of possible carbon monoxide production. This may be a step in the right direction but only for the two mentioned anesthetics, and only as a warning that a possible threat is developing. It may be possible that small electrochemical sensors provide a solution to this problem, judging from the claims of the manufacturers that they are specific and sensitive, presenting an accurate amount of ppm carbon monoxide in a display[53].

Compound A as reaction product of sevoflurane with carbon dioxide absorbents

Sevoflurane is a clear nonflammable liquid with little or no pungent odor. It is a methyl-isopropyl ether with a blood-gas partition coefficient of 0.6-0.7 approaching that of N_2O. Sevoflurane is stable when stored at room temperature but unstable when used in an anesthetic circuit, in both in vivo and in vitro conditions. It degrades by an exothermic reaction with the carbon dioxide absorbent, whereby sevoflurane is dehydrofluronated to produce fluoromethyl-2,2-difluoro-1-(trifluoromethyl)vinyl ether, also known as compound A (CA). A parallel reaction hydrolyses sevoflurane to yield formaldehyde and hydrofluoric acid, with methanol formed from the formaldehyde through a Cannizzaro reaction. Methanol then combines with Compound A to form Compound B, which is subsequently dehydrofluronated to yield Compounds C through E, liberating additional water and hydrofluoric acid in the process. A reaction scheme of this degradation of sevoflurane to compounds A to E as published by Cunningham et al.[54] is shown in figure 1.4, Morio et al.[55] and demonstrated that the magnitude of CA production depends on the temperature.

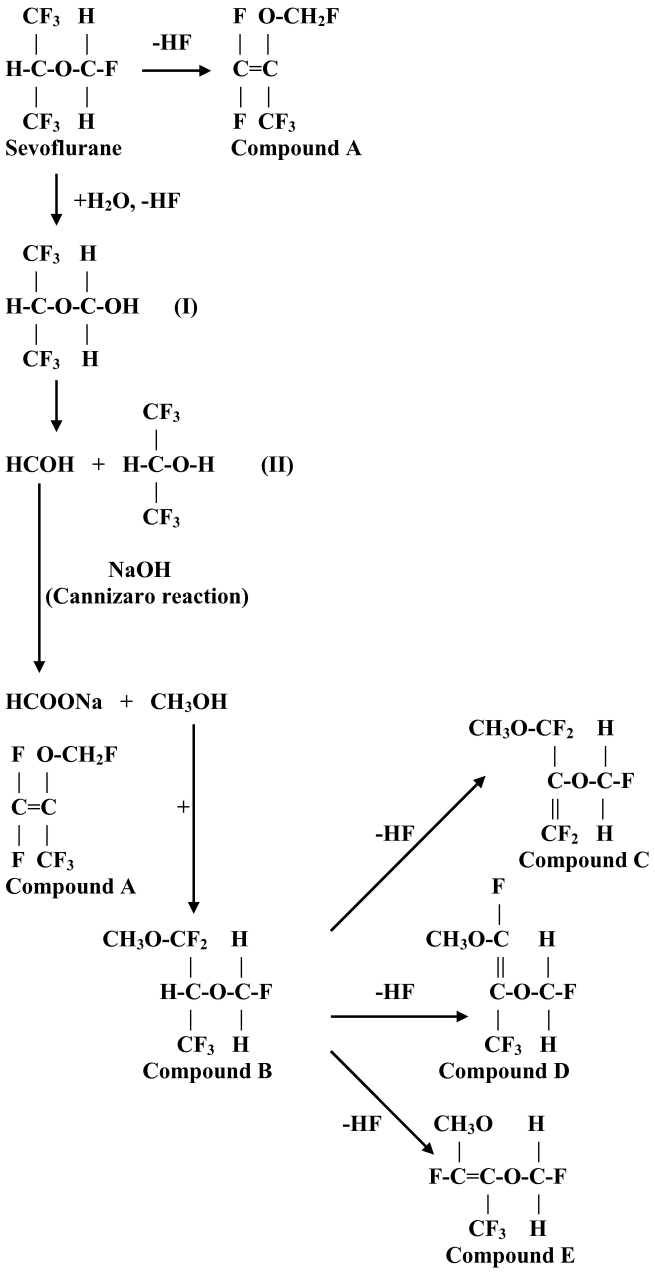


Figure 1.4 Reaction scheme for the degradation of sevoflurane in the presence of base. From Cunningham DD: Sevoflurane degradation to compound A in anesthesia breathing systems. Br.J.Anaesth. 1996;77:537-534, figure 1.

Nephrotoxicity of compound A

From several publications[56-59] it is known that Compound A is nephrotoxic in rats and that this nephrotoxicity is due to a β-lyase mediated metabolization of CA. Histological signs of renal injury have been demonstrated in Wistar rats after a 3-hour exposure to 50 ppm CA[60] or after a 1-hour exposure to 200 ppm CA[61]. Several in vivo studies by Bito et al.[62-67] demonstrated CA production

of 13 to 30 ppm with sevoflurane anesthesia where a higher fresh gas flow resulted in a lower CA production. Conzen et al.[68] measured an exposure of 44 ppm/hour CA during sevoflurane anesthesia in 116 patients. These in vivo CA concentrations are close to the toxic concentrations for rats, but in several in vivo studies[65;66;68-72] where a total of 2176 patients received sevoflurane anesthesia, no adverse effect on renal function could be established. This could be explained by the 8-30 times less active β-lyase pathway in human kidneys than in rat kidneys[73]. However, two studies[74;75] revealed some transient nephrotoxicity in healthy volunteers (n=30) when exposed to a total concentration of more than 80-240 ppm of CA.

Water content and chemical composition of the carbon dioxide absorbent in relation to compound A production

In the previously discussed studies, compound A was produced using fresh i.e. normally hydrated absorbent. There is, however, some relation with water content as Eger et al.[76] demonstrated. In this in vitro study, the drying of Baralyme® increased CA production while drying of sodalime decreased CA production. However, CA was produced in hydrated and desiccated condition with these two absorbents in each experiment.

As new absorbents were developed to prevent carbon monoxide production, studies followed that demonstrated dependence of CA production on the content of strong bases inside the absorbent[46;77]. Studies that tested recently developed absorbents without the strong bases NaOH and KOH, revealed that only minimal (<5 ppm) concentrations of CA were produced[48;49;78-81].

Aim of this thesis

Most of the described in vitro studies investigating CO production from inhalational anesthetics and carbon dioxide absorbents, were conducted in small vials or cylinders containing the studied absorbent[33;45;46;50]. Through these vials a fresh gas flow was conducted with predominantly high concentrations of volatile anesthetics. This setup was also used for several studies investigating CA production from sevoflurane and carbon dioxide absorbents[46;48;54]. The routine clinical situation inside an operating theatre, however, is far more complex. When a patient receives general anesthesia in an operating theatre, he/she will be ventilated through an anesthesia ventilating circuit where the concentrations of volatile anesthetics and the quantity of fresh gas flow are lower than in the previous described laboratory studies. Woehlck et al.[82] demonstrated that concentration of inhalational anesthetic, quantity of fresh gas flow and quantity of minute ventilation are of significant influence on the amount of CO produced in combination with desiccated absorbent. Other studies[55;83] demonstrated the latter for compound A production from sevoflurane. We therefore developed a patient model in which we connected an anesthesia machine to an artificial lung with a study protocol where inhalational anesthetics, minute ventilation and fresh gas flow were introduced in accordance with clinical practice.

The following research questions will be addressed in this thesis:

1) Will al modern inhalational anesthetics produce carbon monoxide in desiccated sodalime? Based on literature findings, we hypothesize that besides desflurane, enflurane and isoflurane, also halothane and sevoflurane will produce carbon monoxide in desiccated sodalime. Whereas Fang et al.[33] described small carbon monoxide production from halothane and sevoflurane in desiccated sodalime, the actual concentrations of CO were not published. Wissing et al.[45] published data on CO production from sevoflurane and halothane, but here carbon monoxide was measured with an infrared detector that is known

to be less accurate than gas chromatography[84]. We will therefore investigate the carbon monoxide production from all inhalational anesthetics and desiccated sodalime in the previous described patient model by means of gas chromatograph.

2) Which factors contribute to the production of CO and CA in carbon dioxide absorbents? From the described studies in this chapter we hypothesize that carbon monoxide is only produced in desiccated absorbents and that this production is dependent on the concentration of strong bases inside the absorbent. The studies investigating CA production from absorbents also described a relationship with the strong base content of the absorbent, but most studies only investigated fresh i.e. hydrated CO_2 absorbents. Therefore, in this thesis we examined the concentrations of carbon monoxide and compound A produced as a result of interaction between five volatile anesthetics and seven different carbon dioxide absorbents with varying concentrations of strong bases, in hydrated and completely desiccated condition.

3) Which instruments can be used to detect CO or CA production in an anesthetic circuit? Previous studies[33;54] demonstrated increasing production of CO and CA in an environment with higher temperature. We therefore hypothesize that temperature increase can be an indicator of CO or CA production. To establish this possible relationship, we measured temperature inside the absorbent. To detect CO in an anesthetic circuit in a more straightforward and more inexpensive manner than gas chromatography, we investigated the reliability of an electrochemical CO sensor.

The different aims of the studies in the chapters of this thesis are summarized here.

Outline of the dissertation

The aim of the study presented in **chapter 2** is to obtain the maximum concentrations of carbon monoxide produced as a result of interaction between the volatile anesthetics desflurane, enflurane, isoflurane, halothane and sevoflurane and completely desiccated sodalime compared to fresh sodalime. Also the temperature inside the absorbent was measured to establish the relationship between CO production and temperature increase as reported in literature[33].

To determine the relation between the content of strong bases inside the carbon dioxide absorbent and the amount of carbon monoxide production, we investigated six different types of desiccated and hydrated absorbents with different concentrations of strong bases in **chapter 3**. Here we used desflurane from which it is known that it produces the highest amounts of carbon monoxide when it comes in contact with desiccated absorbent.

The presented study in **chapter 4** was set up to measure the maximum concentrations of compound A and carbon monoxide, produced as a result of interaction between sevoflurane and seven different type of carbon dioxide absorbents in hydrated and completely desiccated condition. The carbon dioxide absorbents used in this study had different concentrations of strong bases, in order to establish the relationship between CA and CO production and strong base content. Temperature was measured inside the absorbent to obtain the maximum temperature increases of the different absorbents as a result of sevoflurane degradation.

To investigate if an electrochemical carbon monoxide sensor can provide an early warning sign of ongoing carbon monoxide production in an anesthesia machine we studied the reliability of a Bedfont EC-40 electrochemical CO sensor compared to the gold standard i.e. gas chromatography in **chapter 5**. To test the reliability of this sensor with different concentrations of carbon monoxide

we used the inhalational anesthetics desflurane, enflurane, isoflurane, halothane and sevoflurane in combination with completely desiccated sodalime.

After these laboratory studies, where we obtained the maximum concentrations of CO and CA possible for different absorbents, we investigated the average production of CO and CA in anesthetic practice in the VU University Medical Center, where we use Drägersorb 800 plus® as carbon dioxide absorbent. For that purpose, we registered the produced CO and CA concentrations in forty patients receiving desflurane or sevoflurane anesthesia in **chapter 6**.

In **chapter 7** the main conclusions and a general discussion on the results of this thesis are presented.

Reference List

1. Sharp JH, Trudell JR, Cohen EN: Volatile metabolites and decomposition products of halothane in man. Anesthesiology 1979; 50: 2-8
2. Nitric oxide. Encyclopædia Britannica Article , article-9055939. 2007.
3. Priestley J: The discovery of nitrous oxide [1772], Foundations of Anesthesiology. Edited by Faulconer A, Jr., Keys T. Wood Library -Museum of Anesthesiology, 1993, pp 375-84
4. Wells H: Nitrous oxide and Ether [1847], Foundations of Anesthesiology. Edited by Faulconer A, Jr., Keys T. Wood Library -Museum of Anesthesiology, 1993, pp 408-22
5. Faulconer A, Jr., Keys T: Agents - Ether Introduction, Foundations of Anesthesiology. Edited by Faulconer A, Jr., Keys T. Wood Library -Museum of Anesthesiology, 1993, pp 263-5
6. Faulconer AJr, Keys T: Paracelcus, Foundations of Anesthesiology. Edited by Faulconer AJr, Keys T. Wood Library -Museum of Anesthesiology, 1993, p 266
7. Long C: An account of the First Use of Sulphuric Ether by Inhalation as an Anesthetic in Surgical Operations [1849], Foundations of Anesthesiology. Edited by Faulconer A, Jr., Keys T. Wood Library -Museum of Anesthesiology, 1993, pp 310-6
8. Morton W: Remarks on the Proper Mode of Administering Sulphuric Ether by Inhalation [1847], Foundations of Anesthesiology. Edited by Faulconer A, Jr., Keys T. Wood Library -Museum of Anesthesiology, 1993, pp 296-309
9. Guthrie S: New Mode of Preparing a Spirituous Solution of Chloric Ether [1831], Foundations of Anesthesiology. Edited by Faulconer A, Jr., Keys T. Wood Library -Museum of Anesthesiology, 1993, pp 444-6
10. Souberain E: The Action of Chloride of Lime upon Alcohol [1831], Foundations of Anesthesiology. Edited by Faulconer A, Jr., Keys T. Wood Library -Museum of Anesthesiology, 1993, pp 448-53
11. Liebig Jv: Chloroform [1832], Foundations of Anesthesiology. Edited by Faulconer A, Jr., Keys T. Wood Library -Museum of Anesthesiology, 1993, pp 455-8
12. Simpson J: On a New Anaesthetic Agent, More Efficient Than Sulphuric Ether [1847], Foundations of Anesthesiology. Edited by Faulconer A, Jr., Keys T. Wood Library -Museum of Anesthesiology, 1993, pp 463-8
13. Black J: Experiments Upon Magnesia Alba, Quicklime, and Some Other Alcaline Substances [1755], Foundations of Anesthesiology. Edited by Faulconer A, Jr., Keys T. Wood Library -Museum of Anesthesiology, 1993, pp 33-7
14. Coleman A: Mr. Coleman's economising apparatus for re-inhaling the gas. Br J Den Sci 1869; 12: 443
15. Benedict F, Tower O: The Use of Compressed Oxygen in Elementary Organic Analysis and of Soda-Lime in the Quantitative Determination of Carbon Dioxide [1899], Foundations of Anesthesiology. Edited by Faulconer A, Jr., Keys T. Wood Library -Museum of Anesthesiology, 1993, pp 628-9
16. Jackson D: A New Method for the Production of General Analgesia and Anaesthesia With a Description of the Apparatus Used [1915], Foundations of Anesthesiology. Edited by Faulconer A, Jr., Keys T. Wood Library -Museum of Anesthesiology, 1993, pp 630-44
17. Waters R: Clinical Scope and Utility of Carbon Dioxid Filtration in Inhalation Anesthesia [1924], Foundations of Anesthesiology. Edited by Faulconer A, Jr., Keys T. Wood Library -Museum of Anesthesiology, 1993, pp 646-9
18. Sword B: The Closed Circle Method of Administration of Gas Anesthesia [1930], Foundations of Anesthesiology. Edited by Faulconer A, Jr., Keys T. Wood Library -Museum of Anesthesiology, 1993, pp 650-6
19. Coburn RF: Endogenous carbon monoxide production. N.Engl.J.Med. 1970; 282: 207-9
20. Altman C: AANA journal course: update for nurse anesthetists--carbon monoxide poisoning: role of the anesthesia machine's carbon dioxide absorption system. AANA.J. 1996; 64: 41-7
21. Luomanmaki K, Coburn RF: Effects of metabolism and distribution of carbon monoxide on blood and body stores. Am.J.Physiol 1969; 217: 354-63
22. Barker SJ, Tremper KK: The effect of carbon monoxide inhalation on pulse oximetry and transcutaneous PO2. Anesthesiology 1987; 66: 677-9
23. Zhu NH, Weiss HR: Oxy- and carboxyhemoglobin saturation determination in frozen small vessels. Am.J.Physiol 1991; 260: H626-H631
24. Barker SJ, Curry J, Redford D, Morgan S: Measurement of Carboxyhemoglobin and Methemoglobin by Pulse Oximetry: A Human Volunteer Study. Anesthesiology 2006; 105: 892-7
25. Middleton V, Van Poznak A, Artusio JF, Jr., Smith SM: Carbon monoxide accumulation in closed circle anesthesia systems. Anesthesiology 1965; 26: 715-9

26. Morita S, Latta W, Hambro K, Snider MT: Accumulation of methane, acetone, and nitrogen in the inspired gas during closed-circuit anesthesia. Anesth.Analg. 1985; 64: 343-7
27. Moon R, Meyer A, Scott D, Fox E, Millington D, Norwood D: Intraoperative carbon monoxide toxicity. Anesthesiology 1990; 73: A1089
28. Moon R, Ingram C, Brunner E, Meyer A: Spontaneous generation of carbon monoxide within anesthetic circuits. Anesthesiology 1991; 75: A873
29. Epstein RA: Carbon monoxide: what should we do? APSF Newsletter 1994; 9: 37-41
30. Fang ZX, Eger EI: Factors causing the production of carbon monoxide from the action of carbon dioxide absorbents on volatile anesthetics. APSF Newsletter 1994; 9: 25-8
31. Lentz R: CO poisoning during anesthesia poses puzzles. APSF Newsletter 1994; 9: 13-4
32. Moon R: Cause of CO poisoning, relation to halogenated agents still not clear. APSF Newsletter 1994; 9: 13-6
33. Fang ZX, Eger EI, Laster MJ, Chortkoff BS, Kandel L, Ionescu P: Carbon monoxide production from degradation of desflurane, enflurane, isoflurane, halothane, and sevoflurane by soda lime and Baralyme. Anesth.Analg. 1995; 80: 1187-93
34. Frink EJ, Jr., Nogami WM, Morgan SE, Salmon RC: Desflurane anesthesia using dry baralyme produces high carboxyhemoglobin in pings. Anesthesiology 1995; V83: A294
35. Frink EJ, Jr., Nogami WM, Morgan SE, Salmon RC: High carboxyhemoglobin concentrations occur in swine during desflurane anesthesia in the presence of partially dried carbon dioxide absorbents. Anesthesiology 1997; 87: 308-16
36. Bonome, C, Alvarez, F, Soro, M, Belda J, Maestro, M, and Cortes, A. Experimental study about carbon monoxide production with two halogenated agents. Br.J.Anaesth. 78, A67. 1997.
37. Soro, M, Alvarez, F, Bonome, C, Cortes, A., Belda, F. J., and Maestro, M. Time course of soda lime dehydration within the canister in rebreathing circuits with continuous flow. Br.J.Anaesth. 78, A68. 1997.
38. Bonome C, Belda J, Alvarez-Refojo F, Soro M, Fernandez-Goti C, Cortes A: Low-flow anesthesia and reduced animal size increase carboxyhemoglobin levels in swine during desflurane and isoflurane breakdown in dried soda lime. Anesth.Analg. 1999; 89: 909-16
39. Baum J, Sachs G, vd DC, Stanke HG: Carbon monoxide generation in carbon dioxide absorbents. Anesth.Analg. 1995; 81: 144-6
40. Harrison N, Knowles AC, Welchew EA: Carbon monoxide within circle systems. Anaesthesia 1996; 51: 1037-40
41. Hendrickx JF, Soetens M, De Vel M, Van der AP, De Wolf AM: Carboxyhemoglobin concentrations during desflurane and isoflurane closed-circuit anesthesia. Acta Anaesthesiol.Belg. 1996; 47: 67-72
42. Berry PD, Sessler DI, Larson MD: Severe carbon monoxide poisoning during desflurane anesthesia. Anesthesiology 1999; 90: 613-6
43. Baxter PJ, Garton K, Kharasch ED: Mechanistic aspects of carbon monoxide formation from volatile anesthetics. Anesthesiology 1998; 89: 929-41
44. Strauss JM, Baum J, Sumpelmann R, Krohn S, Callies A: Degradation of halothane, enflurane, and isoflurane by dry soda lime to give carbon monoxide. Anaesthesist 1996; 45: 798-801
45. Wissing H, Kuhn I, Warnken U, Dudziak R: Carbon monoxide production from desflurane, enflurane, halothane, isoflurane, and sevoflurane with dry soda lime. Anesthesiology 2001; 95: 1205-12
46. Neumann MA, Laster MJ, Weiskopf RB, Gong DH, Dudziak R, Forster H, Eger EI: The elimination of sodium and potassium hydroxides from desiccated soda lime diminishes degradation of desflurane to carbon monoxide and sevoflurane to compound A but does not compromise carbon dioxide absorption. Anesth.Analg. 1999; 89: 768-73
47. Murray JM, Renfrew CW, Bedi A, McCrystal CB, Jones DS, Fee JP: Amsorb: a new carbon dioxide absorbent for use in anesthetic breathing systems. Anesthesiology 1999; 91: 1342-8
48. Stabernack CR, Brown R, Laster MJ, Dudziak R, Eger EI: Absorbents differ enormously in their capacity to produce compound A and carbon monoxide. Anesth.Analg. 2000; 90: 1428-35
49. Kharasch ED, Powers KM, Artru AA: Comparison of Amsorb, sodalime, and Baralyme degradation of volatile anesthetics and formation of carbon monoxide and compound a in swine in vivo. Anesthesiology 2002; 96: 173-82
50. Knolle E, Heinze G, Gilly H: Small carbon monoxide formation in absorbents does not correlate with small carbon dioxide absorption. Anesth.Analg. 2002; 95: 650-5, table
51. Woehlck HJ, Dunning M, III, Gandhi S, Chang D, Milosavljevic D: Indirect detection of intraoperative carbon monoxide exposure by mass spectrometry during isoflurane anesthesia. Anesthesiology 1995; 83: 213-7
52. Woehlck HJ, Dunning M, III, Nithipatikom K, Kulier AH, Henry DW: Mass spectrometry provides warning of carbon monoxide exposure via trifluoromethane. Anesthesiology 1996; 84: 1489-93
53. Dunning M, III, Woehlck HJ: Performance of an electrochemical carbon monoxide monitor in the presence of anesthetic gases. J.Clin.Monit. 1997; 13: 357-62

54. Cunningham DD, Huang S, Webster J, Mayoral J, Grabenkort RW: Sevoflurane degradation to compound A in anaesthesia breathing systems. Br.J.Anaesth. 1996; 77: 537-43
55. Morio M, Fujii K, Satoh N, Imai M, Kawakami U, Mizuno T, Kawai Y, Ogasawara Y, Tamura T, Negishi A, .: Reaction of sevoflurane and its degradation products with soda lime. Toxicity of the byproducts. Anesthesiology 1992; 77: 1155-64
56. Kharasch ED, Thorning D, Garton K, Hankins DC, Kilty CG: Role of renal cysteine conjugate beta-lyase in the mechanism of compound A nephrotoxicity in rats. Anesthesiology 1997; 86: 160-71
57. Kharasch ED, Hoffman GM, Thorning D, Hankins DC, Kilty CG: Role of the renal cysteine conjugate beta-lyase pathway in inhaled compound A nephrotoxicity in rats. Anesthesiology 1998; 88: 1624-33
58. Iyer RA, Baggs RB, Anders MW: Nephrotoxicity of the glutathione and cysteine S-conjugates of the sevoflurane degradation product 2-(fluoromethoxy)-1,1,3,3, 3- pentafluoro-1-propene (Compound A) in male Fischer 344 rats. J Pharmacol.Exp.Ther. 1997; 283: 1544-51
59. Jin L, Baillie TA, Davis MR, Kharasch ED: Nephrotoxicity of sevoflurane compound A [fluoromethyl-2,2-difluoro-1- (trifluoromethyl)vinyl ether] in rats: evidence for glutathione and cysteine conjugate formation and the role of renal cysteine conjugate beta-lyase. Biochem.Biophys.Res.Commun. 1995; 210: 498-506
60. Gonsowski CT, Laster MJ, Eger EI, Ferrell LD, Kerschmann RL: Toxicity of compound A in rats. Effect of a 3-hour administration. Anesthesiology 1994; 80: 556-65
61. Kandel L, Laster MJ, Eger EI, Kerschmann RL, Martin J: Nephrotoxicity in rats undergoing a one-hour exposure to compound A. Anesth.Analg. 1995; 81: 559-63
62. Bito H, Ikeda K: Effect of total flow rate on the concentration of degradation products generated by reaction between sevoflurane and soda lime. Br.J.Anaesth. 1995; 74: 667-9
63. Bito H, Ikeda K: Degradation products of sevoflurane during low-flow anaesthesia. Br.J.Anaesth. 1995; 74: 56-9
64. Bito H, Ikeda K: Long-duration, low-flow sevoflurane anesthesia using two carbon dioxide absorbents. Quantification of degradation products in the circuit. Anesthesiology 1994; 81: 340-5
65. Bito H, Ikeda K: Closed-circuit anesthesia with sevoflurane in humans. Effects on renal and hepatic function and concentrations of breakdown products with soda lime in the circuit. Anesthesiology 1994; 80: 71-6
66. Bito H, Ikeuchi Y, Ikeda K: Effects of low-flow sevoflurane anesthesia on renal function: comparison with high-flow sevoflurane anesthesia and low-flow isoflurane anesthesia. Anesthesiology 1997; 86: 1231-7
67. Bito H, Ikeuchi Y, Ikeda K: Effects of the water content of soda lime on compound A concentration in the anesthesia circuit in sevoflurane anesthesia. Anesthesiology 1998; 88: 66-71
68. Conzen PF, Kharasch ED, Czerner SF, Artru AA, Reichle FM, Michalowski P, Rooke GA, Weiss BM, Ebert TJ: Low-flow sevoflurane compared with low-flow isoflurane anesthesia in patients with stable renal insufficiency. Anesthesiology 2002; 97: 578-84
69. Higuchi H, Sumikura H, Sumita S, Arimura S, Takamatsu F, Kanno M, Satoh T: Renal function in patients with high serum fluoride concentrations after prolonged sevoflurane anesthesia. Anesthesiology 1995; 83: 449-58
70. Kharasch ED, Frink EJ, Jr., Zager R, Bowdle TA, Artru A, Nogami WM: Assessment of low-flow sevoflurane and isoflurane effects on renal function using sensitive markers of tubular toxicity. Anesthesiology 1997; 86: 1238-53
71. Ebert TJ, Messana LD, Uhrich TD, Staacke TS: Absence of renal and hepatic toxicity after four hours of 1.25 minimum alveolar anesthetic concentration sevoflurane anesthesia in volunteers. Anesth.Analg. 1998; 86: 662-7
72. Mazze RI, Callan CM, Galvez ST, Delgado-Herrera L, Mayer DB: The effects of sevoflurane on serum creatinine and blood urea nitrogen concentrations: a retrospective, twenty-two-center, comparative evaluation of renal function in adult surgical patients. Anesth.Analg. 2000; 90: 683-8
73. Lash LH, Nelson RM, Van Dyke RA, Anders MW: Purification and characterization of human kidney cytosolic cysteine conjugate beta-lyase activity. Drug Metab Dispos. 1990; 18: 50-4
74. Eger EI, Gong D, Koblin DD, Bowland T, Ionescu P, Laster MJ, Weiskopf RB: Dose-related biochemical markers of renal injury after sevoflurane versus desflurane anesthesia in volunteers. Anesth.Analg. 1997; 85: 1154-63
75. Goldberg ME, Cantillo J, Gratz I, Deal E, Vekeman D, McDougall R, Afshar M, Zafeiridis A, Larijani G: Dose of compound A, not sevoflurane, determines changes in the biochemical markers of renal injury in healthy volunteers. Anesth.Analg. 1999; 88: 437-45
76. Eger EI, Ionescu P, Laster MJ, Weiskopf RB: Baralyme dehydration increases and soda lime dehydration decreases the concentration of compound A resulting from sevoflurane degradation in a standard anesthetic circuit. Anesth.Analg. 1997; 85: 892-8
77. Higuchi H, Adachi Y, Arimura S, Kanno M, Satoh T: Compound A concentrations during low-flow sevoflurane anesthesia correlate directly with the concentration of monovalent bases in carbon dioxide absorbents. Anesth.Analg. 2000; 91: 434-9

78. Forster H, Behne M, Warnken UH, Asskali F, Dudziak R: The use of lithium hydroxide for carbon dioxide absorption prevents formation of compound A during sevoflurane anesthesia. Anaesthesist 2000; 49: 106-12
79. Versichelen LF, Bouche MP, Rolly G, Van Bocxlaer JF, Struys MM, De Leenheer AP, Mortier EP: Only carbon dioxide absorbents free of both NaOH and KOH do not generate compound A during in vitro closed-system sevoflurane: evaluation of five absorbents. Anesthesiology 2001; 95: 750-5
80. Mchaourab A, Arain SR, Ebert TJ: Lack of degradation of sevoflurane by a new carbon dioxide absorbent in humans. Anesthesiology 2001; 94: 1007-9
81. Bouche MP, Versichelen LF, Struys MM, Van Bocxlaer JF, De Leenheer AP, Mortier EP, Rolly G: No compound a formation with Superia during minimal-flow sevoflurane anesthesia: a comparison with Sofnolime. Anesth.Analg 2002; 95: 1680-5
82. Woehlck HJ, Dunning M, III, Raza T, Ruiz F, Bolla B, Zink W: Physical factors affecting the production of carbon monoxide from anesthetic breakdown. Anesthesiology 2001; 94: 453-6
83. Fang ZX, Eger EI: Factors affecting the concentration of compound A resulting from the degradation of sevoflurane by soda lime and Baralyme in a standard anesthetic circuit. Anesth.Analg. 1995; 81: 564-8
84. Pehl B, Teichert U: Bestimmung der Massenkonzentrationen an SO2, NO und CO in rauchgassen mittels elektrochemischer MeBzellen. Staub 1990; 50: 261-3

Chapter 2

Carbon monoxide production from five volatile anesthetics in dry sodalime in a patient model: halothane and sevoflurane do produce carbon monoxide; temperature is a poor predictor of carbon monoxide production

---

Christiaan Keijzer, Roberto S.G.M. Perez, Jaap J. de Lange

BMC Anesthesiology 2005; 5:6

Abstract

Background: Desflurane and enflurane have been reported to produce substantial amounts of carbon monoxide (CO) in desiccated sodalime. Isoflurane is said to produce less CO and sevoflurane and halothane should produce no CO at all.

The purpose of this study is to measure the maximum amounts of CO production for all modern volatile anesthetics, with completely dry sodalime. We also tried to establish a relationship between CO production and temperature increase inside the sodalime.

Methods: A patient model was simulated using a circle anesthesia system connected to an artificial lung. Completely desiccated sodalime (950 grams) was used in this system. A low flow anesthesia (500ml/min) was maintained using nitrous oxide with desflurane, enflurane, isoflurane, halothane or sevoflurane. For immediate quantification of CO production a portable gas chromatograph was used. Temperature was measured within the sodalime container.

Results: Peak concentrations of CO were very high with desflurane and enflurane (14262 and 10654 ppm respectively) . It was lower with isoflurane (2512 ppm). We also measured small concentrations of CO for sevoflurane and halothane. No significant temperature increases were detected with high CO productions.

Conclusions: All modern volatile anesthetics produce CO in desiccated sodalime. Sodalime temperature increase is a poor predictor of CO production.

Background

In 1990 first reports were published about carbon monoxide (CO) production in anesthetic circuits[1-3] followed by a few studies that concluded that there was no risk of CO intoxication in common anesthetic practice[4-6]. The potential risk of CO production, however, was clearly established in a laboratory study by Fang et al.[7]. This study was the first to prove that desflurane produced higher amounts of CO compared to enflurane and isoflurane respectively, when in contact with dry sodalime and Baralyme®. Furthermore, they found that Baralyme® produced higher amounts of CO compared to sodalime with all three volatile anesthetics. Frink et al.[8] and Bonome et al.[9] demonstrated in animal studies that desflurane produced high amounts of CO in dry carbon dioxide absorbents, with higher amounts in Baralyme® than sodalime.

In an in vitro study, Wissing et al.[10] found high concentrations of CO production for enflurane and isoflurane as well, and to a lesser extent for sevoflurane and halothane. Wissing et al. further found temperature increase in all analyzed volatile anesthetics, which has been linked to higher production of CO[7]. However, as this study was performed using only a gas flow over a carbon dioxide absorber canister, these results cannot easily be extrapolated to a clinical situation. Furthermore CO measurements were performed with infrared absorption and electrochemical detection which are not as accurate as gas chromatography[11].

Therefore, the purpose of this study is to measure in a simulated patient model, the maximum amounts of CO production for all modern volatile anesthetics, with completely dry sodalime using a gas chromatograph. Also, temperature of the system was measured to establish the relationship between CO production and temperature increase.

Methods

Patient model

Two sample lines were connected to the Y-piece of the circle system: one to a small lumen gas chromatography sample line connected to the gas chromatograph, and one connected to the infrared anesthetic vapor analyzer (SAM, Marquette) sampling at 200 ml/min.

The volatile anesthetics and the sodalime (Drägersorb® 800 plus, composition: 0.003% KOH, 2% NaOH, 82% $Ca(OH)_2$ and 16% H_2O) were obtained from our own stock. The sodalime was dried completely by using an oxygen flow of 15 l/min in sealed glass containers until no more weight reduction could be measured. A 16% weight reduction was established confirming the producer's specifications.

Experiments

For each anesthetic vapor, an experiment was performed in which 950 grams of dry sodalime was used. The ventilator was set in IPPV mode with a tidal volume of 600 ml, a frequency of 14/min and 5 cm H_2O of PEEP. After an equilibration with 40 % oxygen and 60% nitrous oxide was established at a fresh gas flow (FGF) of 5 l/min, anesthetic vapor was introduced by a standard vaporizer. The dial was set until the vapor analyzer showed the target concentration of anesthetic vapor, after which the FGF was reduced to 500 ml/min. For the different anesthetic vapors equilibrium was maintained of 0.45 vol% halothane, 0.6% enflurane, 0.6% isoflurane, 0.8% sevoflurane and 3.0% of desflurane during an experiment.

Carbon monoxide measurements

A portable gas chromatograph (Varian Chrompack CP 2003P) with a TCD detector and a Mollsieve 5A column was used for CO quantification with a lower limit of 1 ppm. This gas chromatograph

(GC) is capable of automatic sampling and was programmed to sample approximately every five minutes during an experiment (a total of 36 samples). The GC was calibrated with two calibration mixtures of 210 and 981 parts per million (ppm) CO in nitrogen (Hoekloos specialty gasses, Dieren). The GC was connected to a desktop PC for control of the GC and data recording, analysis and storage.

Temperature measurements

The sodalime container of the circle system was equipped with temperature probes in the upper and lower layer of the container, temperature data were continuously recorded (samplefrequency 30 Hz) during each experiment.

Analysis of data

The total amount of CO production and absorbent temperature were measured for each of the five volatile anesthetics. All experiments were performed in duplicate (ten experiments in total) in order to verify the reproducibility of the CO measurements. To verify that no CO was produced in normal circumstances, i.e. with fresh sodalime, these measurements were repeated with fresh sodalime.

Analyses were performed with SPSS 11.0. The Mann-Whitney-U was used to assess the reproducibility CO measurements, expressed as lack of significant differences between consecutive measurements, the Kruskal-Wallis and Mann-Whitney-U tests for comparison of CO productions between volatile anesthetics, and temperature change. Data were presented as peak, median and IQR (interquartile range) CO concentrations. For all analyses the significance level was set at 5%.

Results

Carbon monoxide measurements

When the first measurements started different amounts of CO were measured when the sodalime was not sufficiently dried. Therefore each experiment was performed twice and no significant difference was found between consecutive measurements. P-values were for desflurane, enflurane, isoflurane, halothane and sevoflurane respectively: 0.906 , 0.481 , 1.00 , 0.839 , 0.725.

The control experiments with fresh sodalime showed no CO production.

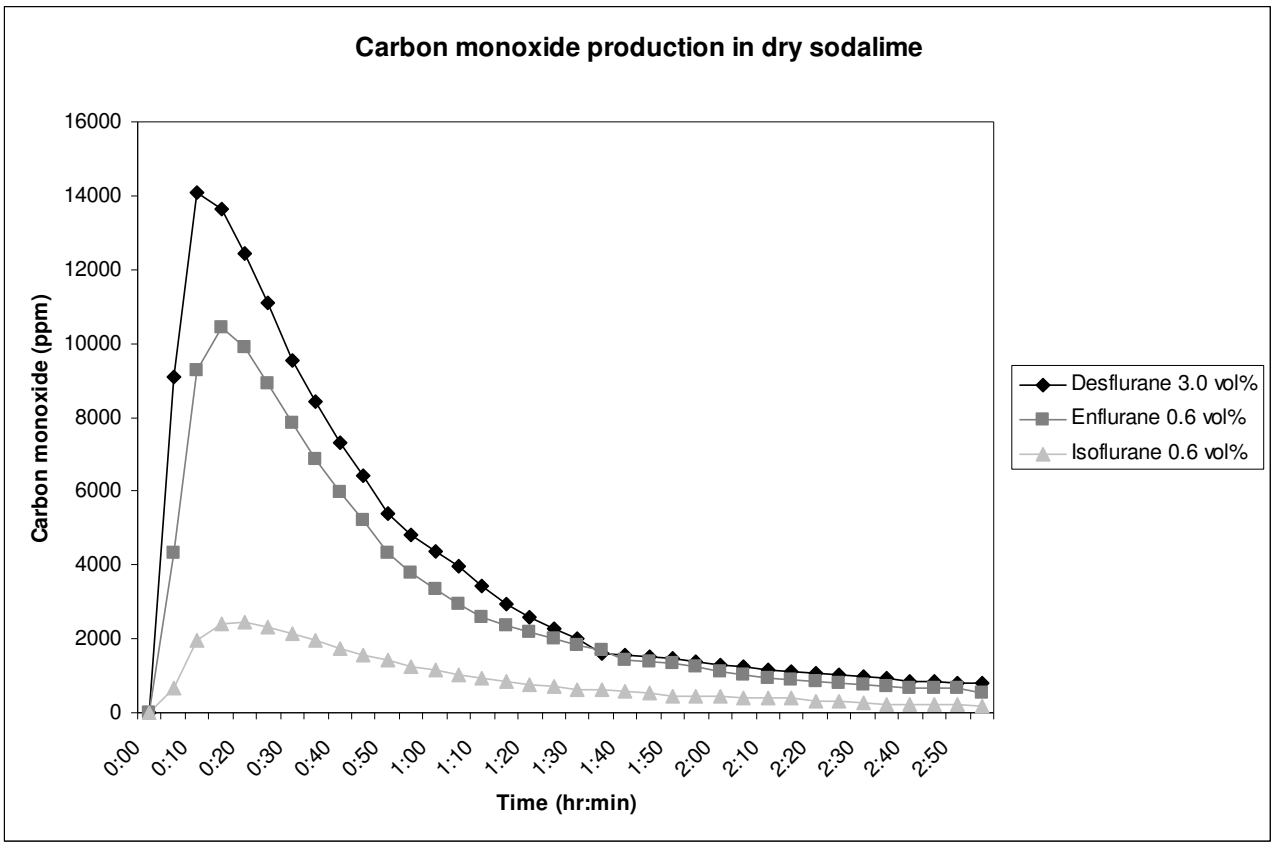


Figure 1. Carbon monoxide production of desflurane, enflurane and isoflurane in desiccated sodalime. Legend: carbon monoxide was measured in parts per million (ppm)

Mean CO concentrations measured by the GC were calculated for each anesthetic vapor. Figure 1 shows the CO concentration for desflurane, isoflurane and enflurane. Because of distinctly lower CO productions for halothane and sevoflurane, both measurements were depicted in a separate

figure (figure 2). A fast increase of CO concentration is seen with shortly after a slow exponential like decrease in concentration.

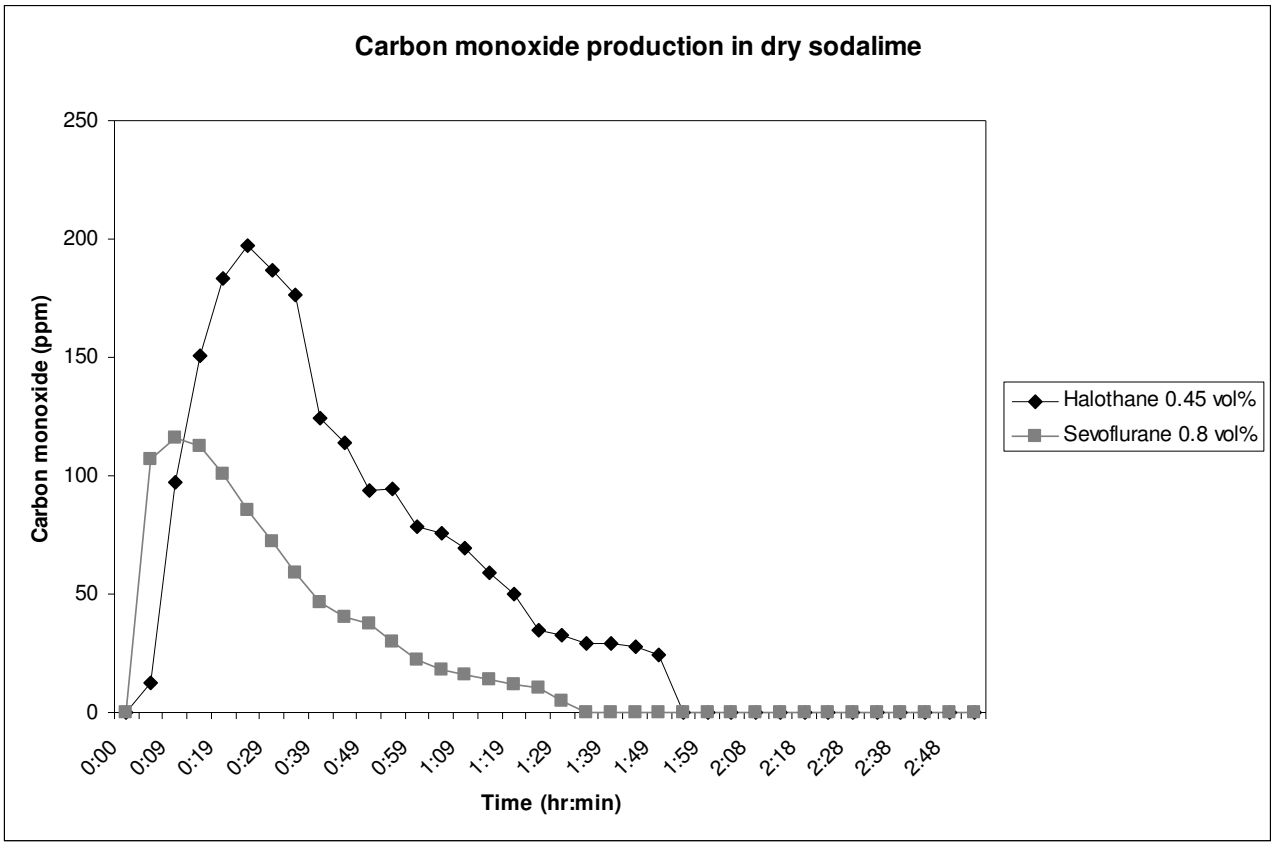


Figure 2. Carbon monoxide production from halothane and sevoflurane in desiccated sodalime. Legend: carbon monoxide was measured in parts per million (ppm)

Complete peak, median and interquartile range (IQR) CO concentrations of all experiments are shown in table 1. Highest CO concentrations in parts per million (ppm) were measured with peak concentrations of 14262±694 for desflurane, followed by 10654±510 for enflurane, 2512±126 for isoflurane and 210±11 for halothane and 121±7 for sevoflurane. Significant differences were found between CO production of the five volatile anesthetics (Kruskall Wallis: $p < 0.001$). Except for the comparison between desflurane - enflurane (Mann-Whitney-U: $p = 0.303$) and halothane - sevoflurane (Mann-Whitney-U: $p = 0.079$) all paired comparisons were significantly different (Mann-Whitney-U: all $p < 0.001$).

Table 1: Carbon monoxide concentrations.

Anesthetic vapor	Peak [CO] ex.1	Peak [CO] ex.2	Median [CO] ex.1	Median [CO] ex.2
Desflurane	13889	14262	1809 (1092-5947)	1816 (1050-6378)
Enflurane	10187	10654	1485 (793-4490)	2044 (892-4394)
Isoflurane	2512	2382	588 (329-1430)	664 (329-1311)
Halothane	185	210	28 (0-92)	31 (0-94)
Sevoflurane	113	121	0 (0-36)	5 (0-43)

Legend: Peak and median interquartile range carbon monoxide concentration [CO] in parts per million for each experiment: ex.1 =experiment 1, ex.2=experiment 2, both with desflurane 3.0 vol%, enflurane 0.6 vol%, isoflurane 0.6 vol%, halothane 0.45 vol% and sevoflurane 0.8 vol% in completely dry sodalime.

Temperature measurements

The temperature measurements at the bottom of the sodalime container showed a mean temperature rise from 23.5 to 28.3 ^{o}C in the experiments with fresh sodalime. In the experiments with dry sodalime (except for sevoflurane) a rise in mean temperature from 24.0 to 32.9 ^{o}C was measured.

In the experiments with dry sodalime and sevoflurane a high increase in temperature from 26.0 to 67.7 ^{o}C was measured during the first twenty minutes. In those twenty minutes the sevoflurane dial had to be set at maximum because otherwise 0.85 vol% sevoflurane could not be maintained in the circle system.

In all experiments a small difference in temperature was seen between the upper and lower layer of the sodalime container with a slightly higher temperature of 0.8 – 1.0 ^{o}C at the bottom of the container.

Discussion

Carbon monoxide production

For this study we developed a method in which a gas chromatograph sampled automatically every five minutes during each experiment, therefore providing the most accurate and reliable CO measurement. To our knowledge this is the first time this kind of setup was used.

In this study the findings of Fang et al.[7], concerning the fact that desflurane produces more CO than enflurane and isoflurane respectively, were confirmed. However, instead of using small vials of 30 ml, we used a patient model, therefore measuring the maximum amounts of CO in completely dry sodalime at a concentration equivalent of approximately 1 MAC of volatile anesthetic using a oxygen/nitrous oxide mixture. Regarding the toxicity of CO, the Henderson and Haggard's Index of Toxic effect[12] indicates that one hour of exposure of more than 1500 ppm of CO is dangerous to life. However one should also take into consideration that the CO is not continuously produced in this model in contrast with this index and that CO absorption by a patient is not included in this model. Therefore we can only conclude from our findings that in these extreme conditions very high CO concentrations can be reached for desflurane and enflurane and that isoflurane can produce significant concentrations of CO as well. One should take into consideration that the use of Baralyme® will produce higher levels of CO[7;13], and that carbon dioxide absorption, fresh gas flow and minute volume have small effects on CO production as shown by Woehlck et al.[13]. Because of the relative small effect of carbon dioxide absorption on CO production we didn't add carbon dioxide to our model.

As for the clinical relevancy, one could say that this model uses completely dry sodalime which is not seen very frequently in common anesthetic practice. However, there are reports of severe CO

intoxications[2;3] recently published by Berry et al.[14] with desflurane as anesthetic agent. The highest risk develops when fresh gas flow is maintained in a anesthesia system for a few days. After 41 hours with a 7 l/min fresh gas flow, the soda lime will become critically dry as published by Soro et al.[15]. As there is always a potential risk, one should consider a safety protocol to maintain a proper humidity level inside the carbon dioxide absorbent as proposed by Woehlck et al.[16], especially when using anesthetic agents like desflurane and enflurane. One could also consider the use of more accurate electrochemical CO monitors[17;18] which can detect CO by continuous measuring in the anesthetic circuit. Another possibility is the use of different carbon dioxide absorbents, particularly absorbents with less $Ba(OH)_2$, KOH and NaOH[19;20] that produce relatively safe amounts of CO or have no CO production at all[21;22].

During the desflurane experiments the infrared anesthetic vapor analyzer reported a concentration of enflurane up to 1.0 vol%, which correlated significantly with the measured CO concentration (Spearman's r: 0.805; $p < 0.001$) . This reported enflurane concentration is probably attributable to the production of trifluoromethane that is simultaneously produced with CO[23] and is known to be detected as enflurane by this vapor analyzer[24]. The enflurane detection disappears below a CO concentration of 3400 ppm, which explains why in the isoflurane experiments no 'enflurane' was detected. In case of a 'mixed gas' warning or a unexpected 'enflurane' detection during anesthesia using desflurane, one should consider the possibility of a (high) CO production.

Contrary to reports in literature[7], we found significant amounts of CO with halothane and sevoflurane. Also CO production by both substances is not explained by the mechanism postulated by Baxter et al.[23]. Previously, CO production was reported by Strauss et al.[25] for halothane and Wissing et al.[10] for both sevoflurane and halothane. They reported higher concentrations of CO than found in our study, but at higher concentrations of these two volatile anesthetics and with use of a

KOH containing absorber. Our reported amounts of CO are not dangerous for several hours in healthy individuals, but could be clinically relevant for anemic patients or small children[26;27].

Temperature measurements

No clinically relevant temperature increase was measured during the experiments with dry sodalime and desflurane, enflurane, isoflurane and halothane. This is not concurrent with findings of other authors[10;28]. Our explanation for these differences is the use of higher concentrations of vapor and a higher fresh gas flow used in the experiments of these studies which would give a more exothermic reaction than in our study. We did however measure a forty degrees Celsius temperature increase in the experiments with sevoflurane and dry sodalime. Simultaneously, we noticed a high degree of sevoflurane degradation because of the discrepancy between dial setting of the vaporizer and the measured sevoflurane concentrations in the circle system. This confirms the report of instability of sevoflurane in desiccated sodalime by Funk et al.[29]. We concluded that temperature measurement in the sodalime container is a very poor predictor of CO production because of the high CO production with desflurane with a small increase of temperature and the other way round for sevoflurane. However a study from Holak et al.[27] demonstrated that clinically relevant CO concentrations with the use of Baralyme® do not occur until the absorbent temperature exceeds 80°C. Because of the use of a combination of sevoflurane and nitrous oxide in this study we cannot rule out that higher concentrations of sevoflurane without nitrous oxide would increase the absorbent temperature above a certain threshold where sodalime could also be capable of production of high concentrations of CO or even result in fire or explosions as recently reported with the use of dessicated Baralyme® and sevoflurane[30-32]. Further studies using sevoflurane and other absorbents with temperature measurement inside the absorbents[33] should be performed to determine if these reactions can also occur with other absorbents than Baralyme®.

Conclusions

In this patient model we demonstrated the possible production of very high amounts of CO in dry sodalime with desflurane and enflurane. CO production from isoflurane is less but still significant. Also sevoflurane and halothane can produce small amounts of CO. A report from the vapor analyzer that a mixed gas or a certain amount of enflurane is present when using desflurane suggests that more then 3400 ppm CO is already present in the anesthesia circle system.

When using desflurane one should consider implementing a safety protocol to prevent the sodalime from completely drying out. Another option is the choice for a 'safer' carbon dioxide absorber. Measurement of the soda lime temperature is a poor predictor for CO production in sodalime when using anesthetic vapor in combination with nitrous oxide.

Competing interests

The author(s) declare that they have no competing interests.

Authors' contributions

CK participated in the design of the study, performed all experiments, participated in the statistical analysis and drafted the manuscript. RP participated in the statistical analysis and helped to draft the manuscript. JL participated in the design of the study and helped to draft the manuscript. All authors read and approved the final manuscript.

Reference List

1. Moon R, Meyer A, Scott D, Fox E, Millington D, Norwood D: Intraoperative carbon monoxide toxicity. Anesthesiology 1990; 73: A1089
2. Moon R, Ingram C, Brunner E, Meyer A: Spontaneous generation of carbon monoxide within anesthetic circuits. Anesthesiology 1991; 75: A873
3. Lentz R: CO poisoning during anesthesia poses puzzles. APSF Newsletter 1994; 9: 13-4
4. Davies MW, Potter FA: Carbon monoxide, soda lime and volatile agents. Anaesthesia 1996; 51: 90
5. Harrison N, Knowles AC, Welchew EA: Carbon monoxide within circle systems. Anaesthesia 1996; 51: 1037-40
6. Hendrickx JF, Soetens M, De Vel M, Van der AP, De Wolf AM: Carboxyhemoglobin concentrations during desflurane and isoflurane closed-circuit anesthesia. Acta Anaesthesiol.Belg. 1996; 47: 67-72
7. Fang ZX, Eger EI, Laster MJ, Chortkoff BS, Kandel L, Ionescu P: Carbon monoxide production from degradation of desflurane, enflurane, isoflurane, halothane, and sevoflurane by soda lime and Baralyme. Anesth.Analg. 1995; 80: 1187-93
8. Frink EJ, Jr., Nogami WM, Morgan SE, Salmon RC: High carboxyhemoglobin concentrations occur in swine during desflurane anesthesia in the presence of partially dried carbon dioxide absorbents. Anesthesiology 1997; 87: 308-16
9. Bonome C, Belda J, Alvarez-Refojo F, Soro M, Fernandez-Goti C, Cortes A: Low-flow anesthesia and reduced animal size increase carboxyhemoglobin levels in swine during desflurane and isoflurane breakdown in dried soda lime. Anesth.Analg. 1999; 89: 909-16
10. Wissing H, Kuhn I, Warnken U, Dudziak R: Carbon monoxide production from desflurane, enflurane, halothane, isoflurane, and sevoflurane with dry soda lime. Anesthesiology 2001; 95: 1205-12
11. Pehl B, Teichert U: Bestimmung der Massenkonzentrationen an SO2, NO und CO in rauchgassen mittels elektrochemischer MeBzellen. Staub 1990; 50: 261-3
12. Altman C: AANA journal course: update for nurse anesthetists--carbon monoxide poisoning: role of the anesthesia machine's carbon dioxide absorption system. AANA.J. 1996; 64: 41-7
13. Woehlck HJ, Dunning M, III, Raza T, Ruiz F, Bolla B, Zink W: Physical factors affecting the production of carbon monoxide from anesthetic breakdown. Anesthesiology 2001; 94: 453-6
14. Berry PD, Sessler DI, Larson MD: Severe carbon monoxide poisoning during desflurane anesthesia. Anesthesiology 1999; 90: 613-6
15. Soro, M, Alvarez, F, Bonome, C, Cortes, A., Belda, F. J., and Maestro, M. Time course of soda lime dehydration within the canister in rebreathing circuits with continuous flow. Br.J.Anaesth. 78, A68. 1997.
16. Woehlck HJ, Dunning M, III, Connolly LA: Reduction in the incidence of carbon monoxide exposures in humans undergoing general anesthesia. Anesthesiology 1997; 87: 228-34
17. Dunning M, III, Woehlck HJ: Performance of an electrochemical carbon monoxide monitor in the presence of anesthetic gases. J.Clin.Monit. 1997; 13: 357-62
18. Bermudez JA: Investigation of electrochemical carbon monoxide sensor monitoring of anesthetic gas mixtures. Anesthesiology 2003; 99: 1233-5
19. Neumann MA, Laster MJ, Weiskopf RB, Gong DH, Dudziak R, Forster H, Eger EI: The elimination of sodium and potassium hydroxides from desiccated soda lime diminishes degradation of desflurane to carbon monoxide and sevoflurane to compound A but does not compromise carbon dioxide absorption. Anesth.Analg. 1999; 89: 768-73
20. Stabernack CR, Brown R, Laster MJ, Dudziak R, Eger EI: Absorbents differ enormously in their capacity to produce compound A and carbon monoxide. Anesth.Analg. 2000; 90: 1428-35
21. Murray JM, Renfrew CW, Bedi A, McCrystal CB, Jones DS, Fee JP: Amsorb: a new carbon dioxide absorbent for use in anesthetic breathing systems. Anesthesiology 1999; 91: 1342-8
22. Keijzer C, Perez R, de Lange JJ: Carbon monoxide production from desflurane and six types of carbon dioxide absorbents in a patient model. Acta Anaesthesiol.Scand. 2005; in press:
23. Baxter PJ, Garton K, Kharasch ED: Mechanistic aspects of carbon monoxide formation from volatile anesthetics. Anesthesiology 1998; 89: 929-41
24. Woehlck HJ, Dunning MB, III, Kulier AH, Sasse FJ, Nithipataikom K, Henry DW: The response of anesthetic agent monitors to trifluoromethane warns of the presence of carbon monoxide from anesthetic breakdown. J.Clin.Monit. 1997; 13: 149-55
25. Strauss JM, Baum J, Sumpelmann R, Krohn S, Callies A: [Degradation of halothane, enflurane, and isoflurane by dry soda lime to give carbon monoxide]. Anaesthesist 1996; 45: 798-801
26. Woehlck HJ, Mei D, Dunning MB, III, Ruiz F: Mathematical modeling of carbon monoxide exposures from anesthetic breakdown: effect of subject size, hematocrit, fraction of inspired oxygen, and quantity of carbon monoxide. Anesthesiology 2001; 94: 457-60

27. Holak EJ, Mei DA, Dunning MB, III, Gundamraj R, Noseir R, Zhang L, Woehlck HJ: Carbon monoxide production from sevoflurane breakdown: modeling of exposures under clinical conditions. Anesth.Analg. 2003; 96: 757-64, table
28. Bonome C, Alvarez F, Belda FJ, Soro M, Cortés-Uribe A: Soda Lime temperature monitoring is a reliable warning method of carbon monoxide production during desflurane and isoflurane anesthesia in swine. Anesth.Analg. 1999; 88: S174
29. Funk W, Gruber M, Wild K, Hobbhahn J: Dry soda lime markedly degrades sevoflurane during simulated inhalation induction. Br.J.Anaesth. 1999; 82: 193-8
30. Fatheree RA, Leighton BL: Acute respiratory distress syndrome after an exothermic baralyme-sevoflurane reaction. Anesthesiology 2004; 101: 531-3
31. Wu J, Previte JP, Adler E, Myers T, Ball J, Gunter JB: Spontaneous ignition, explosion, and fire with sevoflurane and barium hydroxide lime. Anesthesiology 2004; 101: 534-7
32. Castro BA, Freedman LA, Craig WL, Lynch III C: Explosion within an anesthesia machine: Baralyme, high fresh gas flows and sevoflurane concentration. Anesthesiology 2004; 101: 537-9
33. Woehlck HJ: Sleeping with uncertainty: anesthetics and desiccated absorbent. Anesthesiology 2004; 101: 276-8

Chapter 3

Carbon monoxide production from desflurane and six types of carbon dioxide absorbents in a patient model

---

Christiaan Keijzer, Roberto S.G.M. Perez, Jaap J. de Lange

Acta Anaesthesiol. Scand. 2005; 49: 815-818

Abstract

Background: Desflurane is known to produce high concentrations of carbon monoxide (CO) in desiccated sodalime or Baralyme®. Desiccated absorbents without strong bases like potassium hydroxide or sodium hydroxide are reported to produce less or no CO at all. The purpose of this study is to compare the concentration of CO in an anesthesia circuit for desflurane with six different types of completely desiccated CO_2 absorbents with less strong bases than sodalime.

Methods: A patient model was simulated using a circle anesthesia system connected to an artificial lung. Completely desiccated CO_2 absorbent (950 grams) was used in this system. A low flow anesthesia (500 ml min^{-1}) was maintained using desflurane. For immediate quantification of CO production a portable gas chromatograph was used.

Results: Peak concentrations of CO were very high in Medisorb® (Datex-Ohmeda, Hoevelaken, The Netherlands) and Spherasorb® (Intersurgical, Uden, The Netherlands) (13317 and 9045 p.p.m., respectively). It was lower with LoFloSorb® (Intersurgical, Uden, The Netherlands) and Superia® (Datex-Ohmeda, Hoevelaken, The Netherlands) (524 and 31 p.p.m., respectively). Amsorb® (Armstrong, Coleraine, N.Ireland) and lithium hydroxide produced no CO at all.

Conclusion: Medisorb® and Spherasorb® are capable of producing large concentrations of CO when desiccated . LoFloSorb® and Superia® produce far less CO under the same conditions. Amsorb® and lithium hydroxide should be considered safe when desiccated.

After first reports from carbon monoxide (CO) intoxications in anesthetic practice[1;2], studies[3] followed that clearly showed increasing CO production from respectively isoflurane, enflurane and desflurane with relatively dry carbon dioxide absorbents. More recent studies[4;5] demonstrated that desiccated absorbents without strong bases like potassium hydroxide (KOH) and sodium hydroxide (NaOH) produce less CO. However most of the desiccated absorbents used in these studies are capable of a CO production generously exceeding a concentration of 1500 parts per million (p.p.m.). Exposure to this concentration of CO during one hour is dangerous to life[6]. Only for Amsorb® (Armstrong, Coleraine, N.Ireland) no CO production has been reported[7].

Recent reports of severe CO intoxications in anesthetic practice[8;9] indicate that there is still a potential risk, which could possibly be prevented by using a different absorbent. No results have been published previously concerning CO formation as result of desflurane in combination with the newer absorbents LoFloSorb® (Intersurgical, Uden, The Netherlands) and Superia® (Datex-Ohmeda, Hoevelaken, The Netherlands). Therefore, the purpose of this study is to accurately measure in a simulated patient model, the concentrations of CO using desflurane in combination with six different types of desiccated carbon dioxide absorbents with different concentrations of strong bases including LoFloSorb® and Superia®.

Materials and Methods

Patient model

To simulate a patient model, we used a circle anesthesia system (Cicero EM, Dräger, Lubeck, Germany) connected to an artificial lung (Demonstrationsthorax, Dräger). Two sample lines were connected to the Y-piece of the circle system: one to the infrared anesthetic vapor analyzer (SAM, Marquette electronics Inc., Milwauke, WI, USA) sampling at 200 ml min^{-1} and one to a small lumen gas chromatography sample line connected to the gas chromatograph. Sampled gas from the outlet of the infrared anesthetic vapor analyzer was returned to the circle anesthesia system.

Six types of carbon dioxide absorbents (table 1) were used. The absorbents were purchased from their manufacturers. Each type of carbon dioxide absorbent was dried completely by using an oxygen flow of 15 l/min in glass containers until no more further weight reduction could be measured. The weight reduction was consistent with the producers specifications of water content of the absorbent.

Table 1: Composition of carbon dioxide absorbents tested.

CO_2 absorbent	$Ca(OH)_2$ (%)	KOH (%)	NaOH (%)	LiOH (%)	H_2O (%)
Medisorb®	81	0.003	1	-	18
Spherasorb®	84.5	0.003	1.5	-	14
Amsorb®	83.2	-	-	-	14.4
LoFloSorb®	84	-	-	-	16
Superia®	79.5	-	-	-	17.5
Lithium hydroxide	-	-	-	99	1

Absorbents obtained from: Datex-Ohmeda (Medisorb®, Superia®), Intersurgical(Sperasorb®,LoFloSorb®), Armstrong (Amsorb®) and Chem2000 (lithium hydroxide). Amsorb® contains 2.4% other chemicals like polyvinylpyrrolidine, calcium chloride and calcium sulphate. Superia® contains 3% other chemicals like magnesiumchloride and alumino silicate.

Experiments

For each absorbent an experiment was performed in which 950 grams of dry absorbent was used, the ventilator was set in IPPV mode with a tidal volume of 600 ml, a frequency of 14/min and 5 cm H_2O of PEEP. After an equilibration with 40 % oxygen and 60% nitrous oxide was established at a

fresh gas flow of 5 l/min, desflurane was introduced by a standard vaporizer. The dial was set at approximately 4% until the vapor analyzer showed approximately 3.0 vol% of desflurane in the anesthetic circuit. Then the fresh gas flow was reduced to 500 ml min^{-1} maintaining an equilibrium of 3.0 vol% of desflurane in the anesthetic circuit during a three hour experiment. The concentration of 3.0 vol% desflurane was derived from the textbook International Practice of Anaesthesia[10], and used in our clinic with good results in combination with 60% nitrous oxide and fentanyl.

All experiments were performed in duplicate (twelve experiments in total) in order to verify the reproducibility of the CO measurements. To verify that no CO was formed in normal circumstances, i.e. with fresh absorbents, these measurements were repeated with each of the absorbents in fresh condition.

Carbon monoxide measurements

Gas was automatically sampled every 5 minutes from the anesthetic circuit at a rate of 100 ml min^{-1} during 10 seconds until 180 minutes for measuring the concentrations of carbon monoxide with a portable gas chromatograph (Varian Chrompack CP 2003P, Varian Analytical Instruments, Bergen op Zoom, The Netherlands) with a high sensitivity thermal conductivity detector (TCD) and a Mollsieve 5A column. Reliable measurement range of this setup is 1 p.p.m. to $1*10^6$ p.p.m. with a margin of error of 10%. The GC was calibrated with two calibration mixtures of 210 and 981 parts per million (p.p.m.) CO in nitrogen (Hoekloos specialty gasses, Dieren, The Netherlands). The calibration with 981 p.p.m. CO confirmed the linearity of the TCD. The GC was connected to a desktop PC for control of the GC and data recording, analysis and storage.

Analysis of data

Analyses were performed with SPSS 11.0 (SPSS, Gorinchem, The Netherlands). The Mann-Whitney-U was used to assess the reproducibility of CO measurements, expressed as lack of significant differences between the 36 CO concentrations of consecutive measurements. The Kruskal-Wallis was used for comparison between median CO concentrations of all absorbents. Data were presented as peak and median concentrations. For all analyses the significance level was set at 5%.

Results

Carbon monoxide measurements

Since there were no differences in the carbon monoxide tensions in the two consecutive measurements for each absorbent (Mann-Whitney-U: $p > 0.05$), the mean of the two values were used for depiction of the experiments with Medisorb® (Datex-Ohmeda, Hoevelaken, The Netherlands), Spherasorb® and LoFloSorb® (Intersurgical, Uden, The Netherlands) (figure 1), and comparison among the six absorbents.

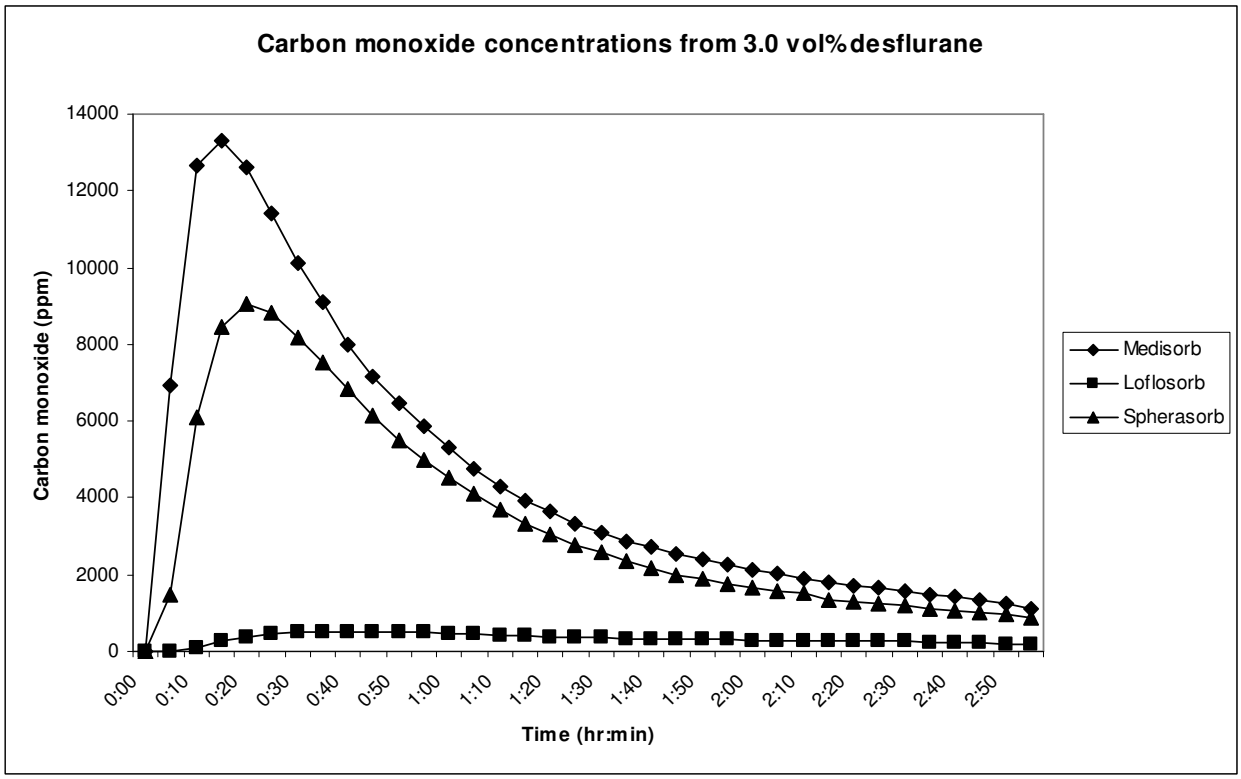


Figure 1. Carbon monoxide concentrations in parts per million from 3.0 vol% desflurane in respectively completely dry Medisorb®, Spherasorb® and LoFloSorb®. Because of the distinctly lower or absent CO concentrations for Superia®, Amsorb® and lithium hydroxide, these measurements are not depicted.

Carbon monoxide concentrations with the absorbents are shown in figure 1. It was not detected with normally hydrated conditions. Both peak and median values of carbon monoxide concentration were highest with Medisorb® and Spherasorb® and it was very low or not detected for LoFloSorb®, Superia®, Amsorb® and lithium hydroxide ($p<0.001$, table 2). Highest concentrations of CO were detected after 15 to 20 minutes (third or fourth sample) for all absorbents except Amsorb® and lithium hydroxide.

Table 2: Mean peak and median carbon monoxide concentration [CO] in parts per million of the two consecutive experiments for each desiccated carbon dioxide absorbent used in combination with desflurane 3.0 vol%.

CO_2 absorbent	Peak [CO]	Median [CO]
Medisorb®	13317	2979
Spherasorb®	9045	2273
LoFloSorb®	525	318
Superia®	32	20
Amsorb®	0	0
Lithium hydroxide	0	0

Significant differences were found between the 36 median CO concentrations of all absorbents (Kruskall Wallis: $p < 0.001$) except for comparison between Medisorb® - Spherasorb® (Mann-Whitney-U: $p = 0.121$) and Amsorb® - LiOH (Mann-Whitney-U: $p = 1.000$).

Interestingly, during the experiments with Medisorb® and Spherasorb® the anesthetic vapor infrared analyzer reported a concentration of enflurane up to 1.2 vol%, which correlated significantly with the measured CO concentration (Spearman's r: 0.98 for Medisorb® and 0.90 for Spherasorb® both with $p<0.001$).

Discussion

Our study provides the maximum concentrations of CO for each desiccated CO_2 absorbent when using 3.0 vol% desflurane with a oxygen/nitrous oxide mixture. Regarding the toxicity of CO, the Henderson and Haggard's Index of Toxic effect[6] indicates that one hour of exposure of more than 1500 p.p.m. of CO is dangerous to life. Therefore our findings show that in these extreme conditions lethal CO concentrations can be reached for Medisorb® and Spherasorb®.

Our study confirms the results from other studies[4;5] that less KOH and, to a lesser extent, NaOH in the carbon dioxide absorbent results in less CO production. However, these studies used 30 ml vials, 21 grams of dry absorbent and 4,3 – 4,5 vol% desflurane without nitrous oxide therefore providing a desflurane concentration below 1 MAC. Our study used a complete circle system with a complete canister of absorbent and 1 MAC desflurane in nitrous oxide, therefore the results are more easily translated to a clinical situation. Another advantage of our study lies in the gas chromatograph we used. This gas chromatograph sampled automatically and online during each experiment, therefore avoiding possible manual sampling and injecting errors. To our knowledge this is the first time this kind of setup was used.

The absorbents used in our study contain no KOH or trace amounts of KOH. The absorbents containing NaOH are responsible for the highest concentrations of CO. However this is not related to the amount of NaOH in the absorbent because Spherasorb® contains more NaOH than Medisorb® and produces less CO. The absorbents completely free of NaOH and KOH produced the smallest

amounts of CO where LoFloSorb® is still capable of producing more than 200 p.p.m. of CO. Superia® generates small but insignificant concentrations of CO and Amsorb® and lithium hydroxide do not produce CO. Possible explanation for the CO production of LoFloSorb® could be the lack of extra ingredients like polyvinylpyrrolidine, calcium chloride and calcium sulfate used in Amsorb® and magnesiumchloride and alumino silicate used in Superia®.

Naturally when using classic sodalime[11] or Baralyme®[5], it would generate higher amounts of CO. Also higher amounts of desflurane (as used in an oxygen/air mixture) would give higher CO concentrations[12]. Less desiccation will result in lower concentrations of CO as published by Frink et al.[13] in a in vivo study with swine. Other parameters like carbon dioxide absorption, fresh gas flow and minute volume have small effects on CO production as shown by Woehlck et al.[14]. Because of the relatively small effect of carbon dioxide absorption on CO production we didn't add carbon dioxide to our model.

The reported enflurane concentration is probably attributable to the production of trifluoromethane that is simultaneously produced with CO[15] and is known to be detected as enflurane by this vapor analyzer[16]. The enflurane detection disappears below a CO concentration of approximately 1800 p.p.m., this explains why in the other experiments no 'enflurane' was detected. In case of a 'mixed gas' warning or a unexpected 'enflurane' detection using desflurane and one of these absorbents, one should consider the possibility of a (high) CO production.

The highest risk for CO formation occurs when fresh gas flow is maintained in an anesthesia system during a few days, because after 41 hours of a 7 l/min fresh gas flow the soda lime will become critically dry[17]. So, if one would like to avoid this potential lethal CO production from desflurane with the carbon dioxide absorbent one should consider using absorbents like Amsorb®, lithium hydroxide or Superia®. Also desiccated LoFloSorb® is not dangerous to life but could generate a mild CO intoxication after three or more hours.

When considering changing the type of absorbent, one should also consider the cost effect, because most newer type of absorbents are more expensive and have a lower CO_2 absorbing capacity. As Stabernack et al.[5] demonstrated, the latter is not the case for lithium hydroxide which has a higher carbon dioxide absorbing capacity but is much more corrosive than the absorbents based on calciumhydroxide and is therefore not available for use in clinical practice. Instead of changing the absorbent, one could also implement a safety protocol to maintain a proper humidity level inside the carbon dioxide absorbent[18], and thus preventing the formation of CO.

Conclusions

In this simulated patient model we demonstrated the possible production of high concentrations of CO in the more classic absorbents Medisorb® and Spherasorb®. LoFloSorb® generates only small amounts of CO. The products Superia®, Amsorb® and Lithium hydroxide should be considered safe to use in combination with desflurane. Because lithium hydroxide is not available for clinical use, only Superia® and Amsorb® are commercially available for anesthesia systems. A report from the vapor analyzer that a mixed gas or a certain amount of enflurane is present when using desflurane suggests that more than 1800 p.p.m. carbon monoxide is already present in the anesthesia circle system.

Reference List

1. Moon R, Meyer A, Scott D, Fox E, Millington D, Norwood D: Intraoperative carbon monoxide toxicity. Anesthesiology 1990; 73: A1089
2. Lentz R: CO poisoning during anesthesia poses puzzles. APSF Newsletter 1994; 9: 13-4
3. Fang ZX, Eger EI, Laster MJ, Chortkoff BS, Kandel L, Ionescu P: Carbon monoxide production from degradation of desflurane, enflurane, isoflurane, halothane, and sevoflurane by soda lime and Baralyme. Anesth.Analg. 1995; 80: 1187-93
4. Neumann MA, Laster MJ, Weiskopf RB, Gong DH, Dudziak R, Forster H, Eger EI: The elimination of sodium and potassium hydroxides from desiccated soda lime diminishes degradation of desflurane to carbon monoxide and sevoflurane to compound A but does not compromise carbon dioxide absorption. Anesth.Analg. 1999; 89: 768-73
5. Stabernack CR, Brown R, Laster MJ, Dudziak R, Eger EI: Absorbents differ enormously in their capacity to produce compound A and carbon monoxide. Anesth.Analg. 2000; 90: 1428-35
6. Altman C: AANA journal course: update for nurse anesthetists--carbon monoxide poisoning: role of the anesthesia machine's carbon dioxide absorption system. AANA.J. 1996; 64: 41-7
7. Murray JM, Renfrew CW, Bedi A, McCrystal CB, Jones DS, Fee JP: Amsorb: a new carbon dioxide absorbent for use in anesthetic breathing systems. Anesthesiology 1999; 91: 1342-8
8. Berry PD, Sessler DI, Larson MD: Severe carbon monoxide poisoning during desflurane anesthesia. Anesthesiology 1999; 90: 613-6
9. Fatheree RA, Leighton BL: Acute respiratory distress syndrome after an exothermic baralyme-sevoflurane reaction. Anesthesiology 2004; 101: 531-3
10. Halsey MJ: Potency, physical properties and molecular mechanisms of inhalational anaesthetics, International Practice of Anaesthesia. Edited by Prys-Roberts C, R Brown Jr B. Butterworth-Heineman, 1996, pp 1-10/1-1/10/15
11. Keijzer, C, Perez, RSGM, and de Lange, J. J. Carbon monoxide production from five volatile anesthetics in dry sodalime in a patiënt model: halothane and sevoflurane do produce carbon monoxide. Eur.J.Anaesthesiol. 32(Supplement), A-841. 2004.
12. Wissing H, Kuhn I, Warnken U, Dudziak R: Carbon monoxide production from desflurane, enflurane, halothane, isoflurane, and sevoflurane with dry soda lime. Anesthesiology 2001; 95: 1205-12
13. Frink EJ, Jr., Nogami WM, Morgan SE, Salmon RC: High carboxyhemoglobin concentrations occur in swine during desflurane anesthesia in the presence of partially dried carbon dioxide absorbents. Anesthesiology 1997; 87: 308-16
14. Woehlck HJ, Dunning M, III, Raza T, Ruiz F, Bolla B, Zink W: Physical factors affecting the production of carbon monoxide from anesthetic breakdown. Anesthesiology 2001; 94: 453-6
15. Baxter PJ, Garton K, Kharasch ED: Mechanistic aspects of carbon monoxide formation from volatile anesthetics. Anesthesiology 1998; 89: 929-41
16. Woehlck HJ, Dunning M, III, Nithipataikom K: Monitoring of isoflurane and desflurane breakdown: interfering gases and infrared detection. J Clin Monit 2000; 16: 535-40
17. Soro, M, Alvarez, F, Bonome, C, Cortes, A., Belda, F. J., and Maestro, M. Time course of soda lime dehydration within the canister in rebreathing circuits with continuous flow. Br.J.Anaesth. 78, A68. 1997.
18. Woehlck HJ, Dunning M, III, Connolly LA: Reduction in the incidence of carbon monoxide exposures in humans undergoing general anesthesia. Anesthesiology 1997; 87: 228-34

Chapter 4

Compound A and carbon monoxide production from sevoflurane and seven different types of carbon dioxide absorbent in a patient model

---

Christiaan Keijzer, Roberto S.G.M. Perez, Jaap J. de Lange

Acta Anaesthesiol. Scand. 2007; 51: 31-37

Abstract

Background: The degradation of sevoflurane can lead to the production of compound A (CA), carbon monoxide (CO), and increase of temperature of the absorbent. CA is known to be nephrotoxic in rats. These reactions depend upon the content of strong bases of the carbon dioxide absorbent used, and it's water content. The purpose of this study is to measure the maximum amounts of CA, CO and temperature increase for seven different carbon dioxide absorbents for sevoflurane with differing contents of strong bases.

Methods: Seven absorbents (some free of strong bases(f)) were used in hydrated(h) and completely desiccated(d) condition in a patient model, using a circle anesthesia system connected to an artificial lung. A low flow anesthesia with an oxygen/nitrous oxide mixture was maintained using 0.8% sevoflurane. For quantification of CA and CO, a portable gas chromatograph was used. Temperature was measured inside the absorbent.

Results: In consecutive order of CA producing potency, Amsorb®(f)(d), Drägersorb®(h), Medisorb®(h), lithiumhydroxide(f)(d), Drägersorb®(d), Medisorb®(d), Spherasorb®(h), Spherasorb®(d), produced small amounts of CA. LoFloSorb® and Superia®, which are free of strong bases, did not produce any CA or CO in hydrated or desiccated condition.

Only desiccated Drägersorb®, Medisorb® and Spherasorb® demonstrated small amounts of CO accompanied by a significant temperature increase.

Conclusion: In this patient model we demonstrated that different types of absorbents produce small amounts of CA and CO or not at all. No relationship could be established between temperature and CA concentration.

Sevoflurane is known to be the most unstable modern volatile anesthetic molecule, and can be degraded in dry sodalime[1;2]. The most important degradation product of sevoflurane is fluoromethyl-2,2-difluoro-1-(trifluoromethyl)vinyl ether (Compound A) which has proved to be nephrotoxic in rats[3;4]. The amount of compound A production depends on the composition of the carbon dioxide absorbent used. Several in vitro studies demonstrated that absorbents with less strong bases like potassium hydroxide (KOH) and sodium hydroxide (NaOH) will result in less compound A (CA) production[5-7]. No results have been published previously concerning CA formation as result of sevoflurane in combination with the newer absorbents LoFloSorb® and desiccated Amsorb® and Superia®, which do not contain any strong bases.

Sevoflurane degradation is accompanied by high temperature increase of the absorbent as reported by Janshon et al.[2] and also extremely high temperatures of more than 200°C have been reported in combination with barium hydroxide containing absorbent Baralyme®[8;9].

There are also studies available that demonstrate production of carbon monoxide (CO) as a result of sevoflurane with sodalime[10;11] and baralyme[8]. On the other hand, absorbents with less strong bases have been reported to produce no CO under any circumstances[12]. No studies have been published regarding possible CO production as a result of interaction between sevoflurane and the absorbents Medisorb®, Spherasorb® (that contains less NaOH than normal sodalime) or LoFloSorb®, Superia® and Lithium hydroxide (which are free of strong bases). Therefore, the purpose of this study is to measure by means of a gas chromatograph, in a simulated patient model, the maximum amounts of CA and CO production, and temperature increase of the absorbent, using sevoflurane in combination with seven different types of completely desiccated and normal hydrated carbon dioxide absorbents with different concentrations of strong bases including the absorbents mentioned above.

Materials and Methods

Patient model

To simulate a patient, we used a semi-closed circle anesthesia system (Cicero EM, Dräger, Lubeck, Germany) connected to an artificial lung (Demonstrationsthorax, Dräger). Two sample lines were connected to the Y-piece: one to the infrared anesthetic vapor analyzer (SAM, Marquette Electronics Inc., Milwaukee, WI, USA) sampling at 200 ml/min and one to a small lumen sample line connected to the gas chromatograph. Sampled gas from the outlet of the infrared anesthetic vapor analyzer was returned to the circle anesthesia system.

Seven different types of carbon dioxide absorbents (table 1) were tested in normally hydrated and desiccated conditions. Each type of carbon dioxide absorbent was dried completely by using an oxygen flow of 15 l/min in glass containers until no more further weight reduction could be measured. The weight reduction was consistent with the producer's specifications of water content of the absorbent. The mean drying time was 47.5 hours ± 2.4.

Table 1: Composition of carbon dioxide absorbents tested.

CO_2 absorbent	$Ca(OH)_2$ (%)	KOH (%)	NaOH (%)	LiOH (%)	H_2O (%)
Drägersorb 800 plus®	82	0.003	2	-	16
Medisorb®	81	0.003	3	-	16
Spherasorb®	84.5	0.003	1.5	-	14
Amsorb®	83.2	-	-	-	14.4
LoFloSorb®	84	-	-	-	16
Superia®	79.5	-	-	-	17.5
Lithium hydroxide	-	-	-	99	1

Absorbents obtained from: Dräger, Lubeck, Germany (Drägersorb 800 plus®), Datex-Ohmeda, Hoevelaken, the Netherlands (Medisorb®, Superia®), Intersurgical, Uden, the Netherlands (Spherasorb®,LoFloSorb®), Armstrong, Coleraine, Northern Ireland (Amsorb®) and Chem2000, Delft, the Netherlands (lithium hydroxide). Amsorb® contains 2.4% other chemicals like polyvinylpyrrolidine, calcium chloride and calcium sulphate. Superia® contains 3% other chemicals like magnesiumchloride and alumino silicate.

Experiments

For each absorbent two experiments were performed: one using 950 grams of dry absorbent and one using 950 grams of normally hydrated absorbent. The ventilator was set in continuous positive

pressure ventilation mode with a tidal volume of 600 ml, a frequency of 14 and 5 cm H_2O of PEEP. After an equilibration with 40 % oxygen and 60% nitrous oxide was established at a fresh gas flow (FGF) of 5 l/min, sevoflurane was introduced by a standard vaporizer. The vaporizer dial was set at 2% until the vapor analyzer showed approximately 0.8% sevoflurane after which the FGF was reduced to 500 ml/min. Equilibrium of 0.8% sevoflurane was maintained during an experiment. The concentration of 0.8% sevoflurane in combination with nitrous oxide results in a total MAC of approximately 1.3 as used in previous studies[13;14]. All experiments were performed in duplicate (28 experiments in total) in order to verify the reproducibility of the CA and CO measurements.

Compound A and carbon monoxide measurements

Gas was automatically sampled every 5 minutes from the anesthetic circuit at a rate of 100 ml/min during 10 seconds up to 180 min for measuring the concentrations of compound A and carbon monoxide with a portable gas chromatograph (Varian Chrompack CP 2003P, Varian Analytical Instruments, Bergen op Zoom, the Netherlands). The gas chromatograph (GC) was equipped with a high sensitivity thermal conductivity detector (TCD) and a Poraplot Q column for isolating CA and a Mollsieve 5A column for isolating CO. The reliable measurement range of this setup is 1 ppm to $1*10^6$ ppm with a margin of error of 10%. The GC was calibrated with a calibration mixture of 12 parts per million (ppm) CA in nitrogen (Scott specialty gasses, Breda, the Netherlands) derived from three millilitres of 99,6% pure CA (Baxter Pharmaceutical Products Inc., New Providence, NJ, USA). Calibration for CO was done with a mixture of 210 ppm CO in nitrogen (Hoekloos specialty gasses, Dieren, the Netherlands), a second mixture of 981 ppm CO in nitrogen confirmed the linearity of the TCD. The gas chromatograph (GC) was connected to a desktop PC for control of the GC and data recording, analysis and storage.

Temperature measurements

The carbon dioxide absorbent container of the circle system was equipped with temperature probes in the upper and lower layer of the container as described in a previous study[11]. Temperature data were continuously recorded (sample frequency 30Hz) during each experiment.

Analysis of data

The total amount of CA and CO concentrations and absorbent temperature were measured for each of the seven carbon dioxide absorbents in normally hydrated and desiccated condition.

Analyzes were performed with SPSS 11.0 using the Mann-Whitney-U test. Reproducibility of the CA and CO measurements was assessed, expressed as lack of significant differences between the 36 CA concentrations of consecutive measurements, and made a comparison between the mean 36 CA concentrations of each absorbent in desiccated versus normally hydrated condition. Data were presented as mean concentrations and as area under the curve calculated with a trapezium method from the mean concentrations from the duplicate experiments. For all analyzes the significance level was set at 5%.

Results

Compound A and carbon monoxide measurements

No significant differences were measured between the compound A and carbon monoxide concentrations in the two consecutive measurements for each absorbent in normally hydrated and desiccated condition (Mann-Whitney U test: $P>0.05$). Therefore, the mean of the two values for CA and CO measurements were used for depiction of the experiments. Only in the experiments with desiccated Drägersorb 800 plus® (data previously published[11]), Medisorb® and Spherasorb® we found low concentrations of CO. Therefore, the results for the CA measurements for these

absorbents in hydrated and desiccated condition were combined with the CO measurements for these absorbents in desiccated condition for Drägersorb 800 plus® (figure 1), Medisorb® (figure 2) and Spherasorb® (figure 3). The CA measurements in hydrated and desiccated condition are shown for Amsorb® (figure 4) and Lithium hydroxide (figure 5). The LoFloSorb® and Superia® experiments were not depicted because no CA or CO production was measured.

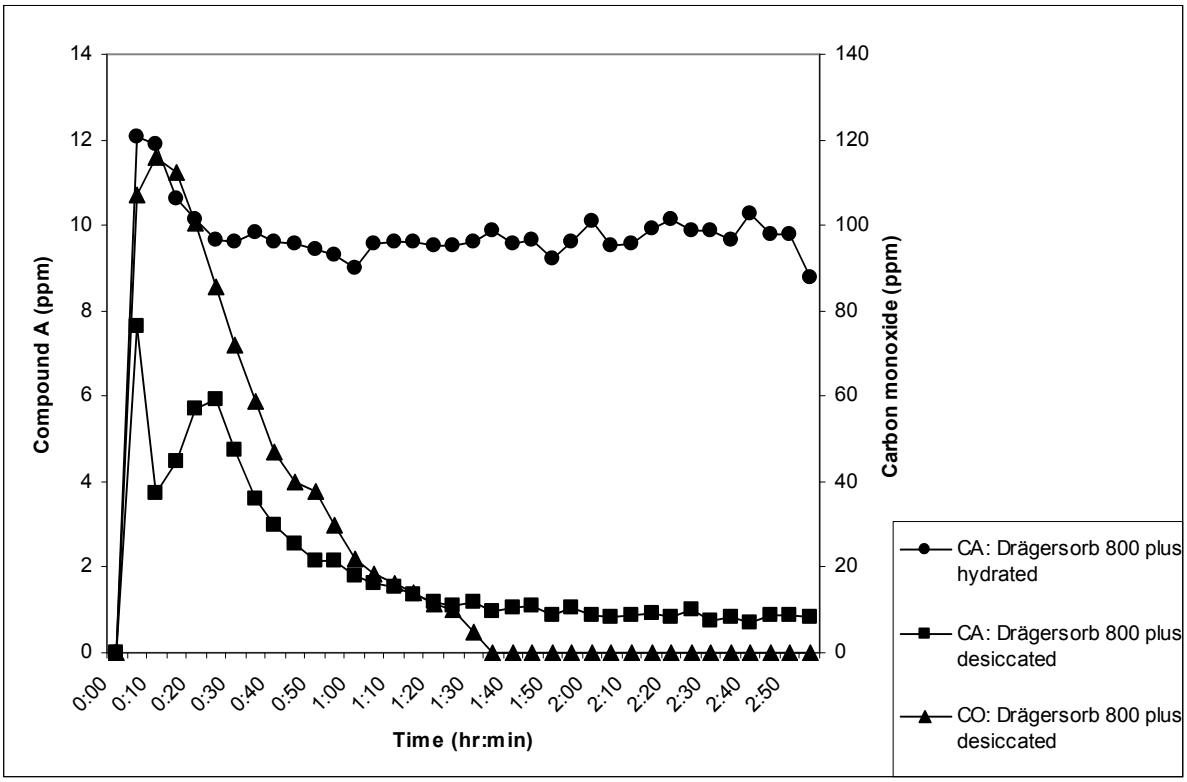


Figure 1. Compound A (CA) and carbon monoxide (CO) concentrations in parts per million (ppm) from 0.8% sevoflurane in normally hydrated and completely dry Drägersorb 800 plus®.

The calculated area's under the curve for compound A were highest for desiccated Amsorb®, normally hydrated Drägersorb 800 plus® and normally hydrated Medisorb® respectively. It was lower for desiccated lithium hydroxide, followed by desiccated Drägersorb 800 plus®, desiccated Medisorb®, normally hydrated Spherasorb® and desiccated Spherasorb®.

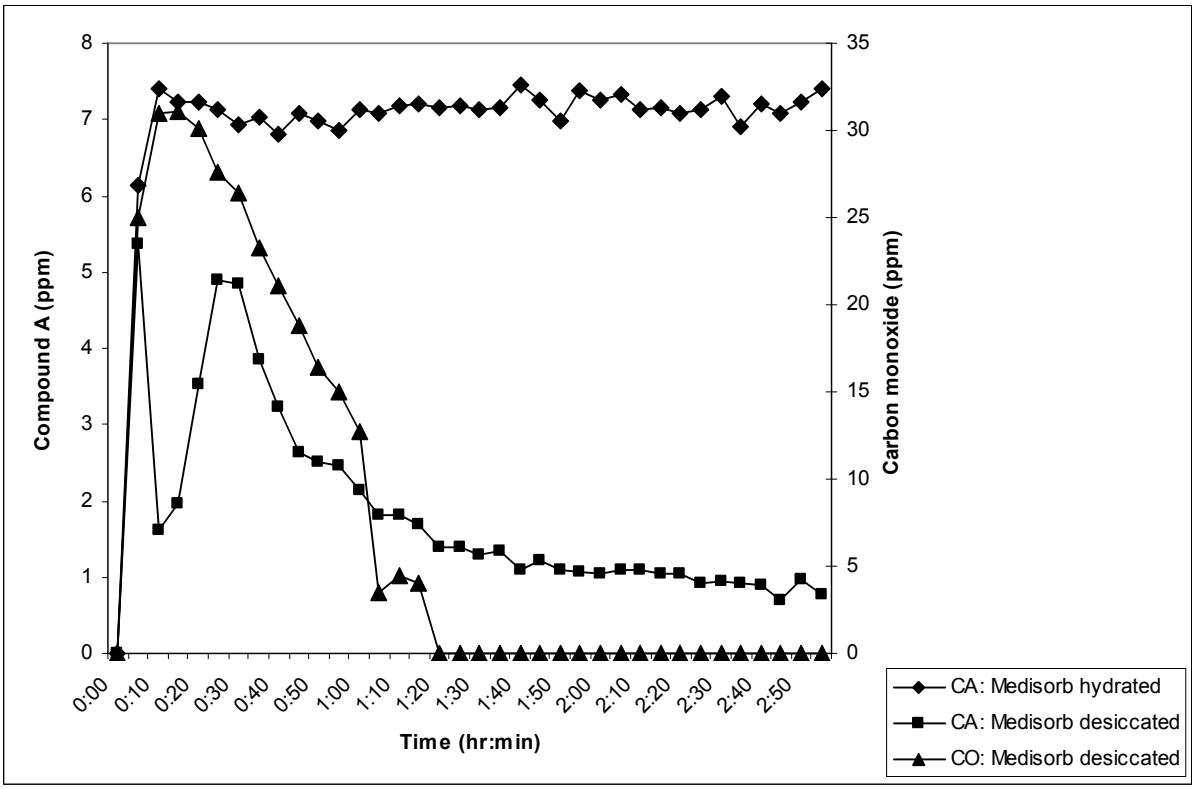


Figure 2. Compound A (CA) and carbon monoxide (CO) concentrations in parts per million (ppm) from 0.8% sevoflurane in normally hydrated and completely dry Medisorb®.

The calculated area's under the curve for carbon monoxide were highest for desiccated Drägersorb 800 plus®, desiccated Spherasorb® and desiccated Medisorb®. The area's under the curve for both CA and CO measurements are shown in table 2.

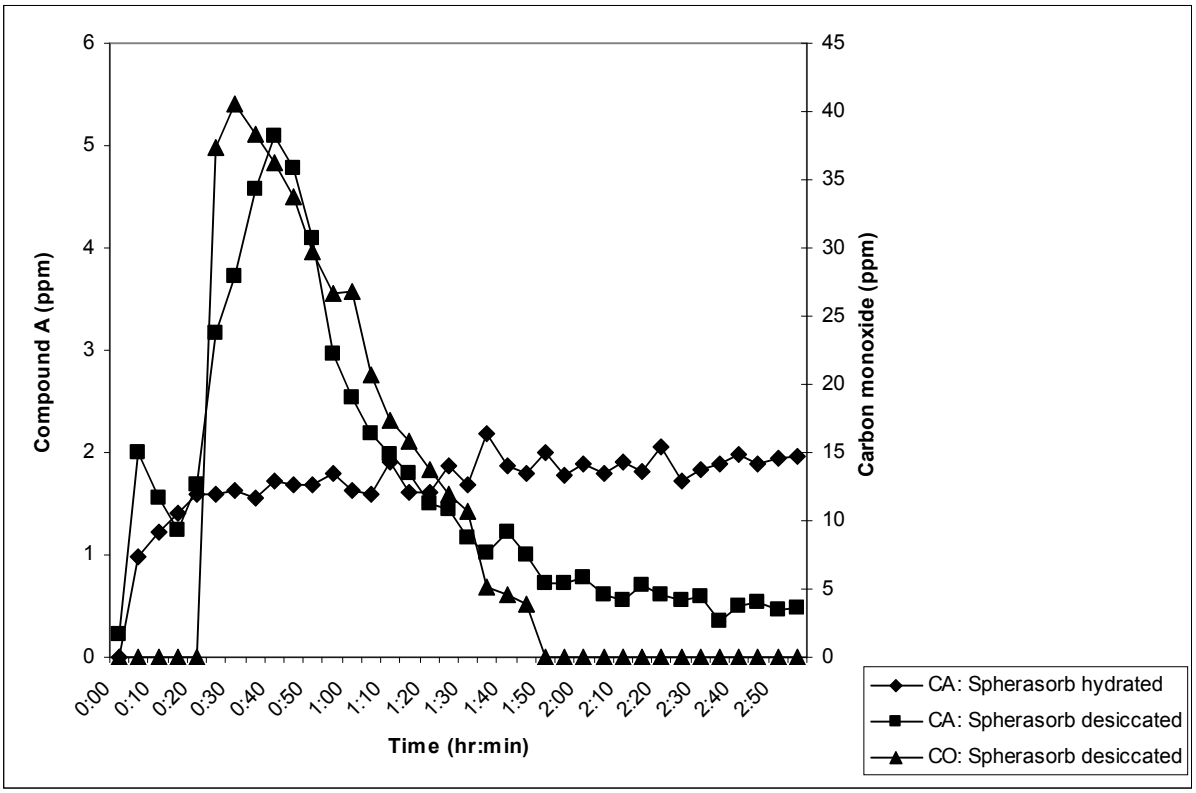


Figure 3. Compound A (CA) and carbon monoxide (CO) concentrations in parts per million (ppm) from 0.8% sevoflurane in normally hydrated and completely dry Spherasorb®.

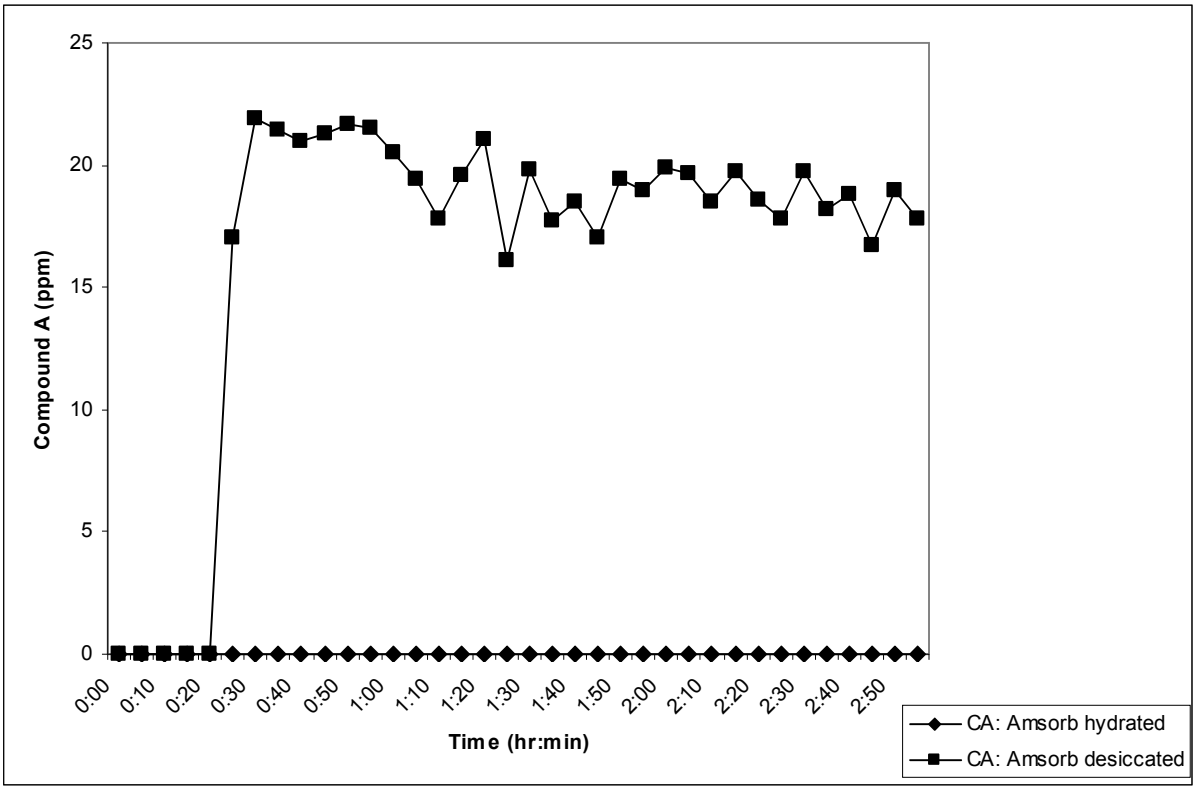


Figure 4. Compound A (CA) concentrations in parts per million (ppm) from 0.8% sevoflurane in normally hydrated and completely dry Amsorb®. This absorbent does not produce any carbon monoxide under any condition.

Temperature measurements

In all experiments a slightly higher temperature of 0.8 – 1.0 °C was measured at the bottom of the absorbent container compared to the upper layer. Ambient room temperature was approximately 19.5 °C and the mean absorbent temperature at the start of the experiments was 23.3 °C ± 2.0.

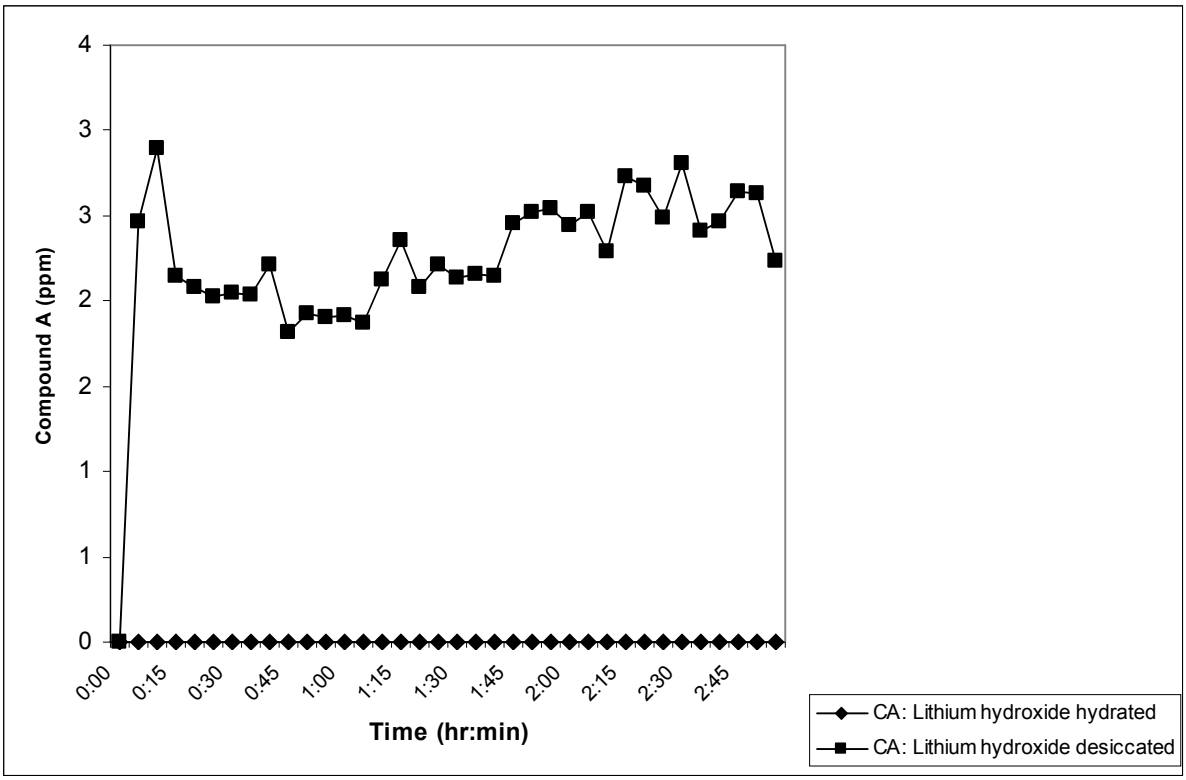


Figure 5. Compound A (CA) concentrations in parts per million (ppm) from 0.8% sevoflurane in normally hydrated and completely dry Lithium hydroxide. This absorbent does not produce any carbon monoxide under any condition.

Only desiccated Drägersorb 800 plus®, Medisorb® and Spherasorb® showed a significant increase in temperature during the first twenty minutes of each experiment. To maintain a concentration of 0.8% sevoflurane during these twenty minutes the sevoflurane dial had to be set at maximum, demonstrating a high degradation rate of sevoflurane. The mean temperature increase during these experiments was 41.7 °C ± 0.6 for Drägersorb 800 plus® (previously published[11]), 32.7 °C ± 0.7 for Medisorb® and 32.8 °C ± 0.5 for Spherasorb®.

For all other experiments a mean temperature increase of 5.1°C ± 1.9 was recorded.

Discussion

Compound A and carbon monoxide production

This study provides the maximum concentrations of CA and CO for each hydrated and desiccated CO_2 absorbent when using 0.8 vol% sevoflurane with an oxygen/nitrous oxide mixture. CA production was relatively low for all absorbents under any condition, with no peak CA concentrations above 22 parts per million.

Table 2: Areas under the curve (AUCs, ppm*min) of compound A (CA) and carbon monoxide (CO) based upon the mean concentrations from the duplicate experiments of each desiccated and normally hydrated carbon dioxide absorbent used in combination with sevoflurane 0.8%.

CO_2 absorbent	AUC-CA-d	AUC-CA-f	AUC-CO-d	AUC-CO-f
Drägersorb 800 plus®	351	1695	4516	0
Medisorb®	327	1228	1452	0
Spherasorb®	294	301	1866	0
LoFloSorb®	0	0	0	0
Superia®	0	0	0	0
Amsorb®	2937	0	0	0
Lithium hydroxide	396	0	0	0

d, desiccated absorbent; f, normally hydrated absorbent.

CO production was only measured in desiccated Drägersorb 800 plus®, Medisorb® and Spherasorb® with peak concentrations not higher than 116 ppm and therefore seems not clinically relevant.

In several in vivo studies[13-17], also small amounts of CA were found under normally hydrated condition of the used absorbents. As comparable results were also found for other base-free absorbents (such as KOH and NaOH) in this study, we can conclude that absorbents with less strong bases produce less CA in hydrated condition[5;7;18].

Little is known about the difference between hydrated and dry absorbents with regard to their capacity to produce CA from sevoflurane. Only Eger et al.[19] demonstrated that drying of Baralyme® increased the CA production, but that drying of classic sodalime decreased the amounts of CA produced. In this study we found a similar reduction of CA concentrations for Drägersorb 800 plus® and Medisorb® in completely dry condition compared to normally hydrated condition. On the other hand, an increase in CA concentration is shown for Spherasorb®, Amsorb® and lithiumhydroxide. A possible explanation for this increase in CA concentration could be the lower concentration or lack of NaOH in these absorbents.

For the absorbents Amsorb® and lithiumhydroxide we can confirm that no CA is produced in normally hydrated conditions[20-22]. One should take into account, however, that Amsorb® is the absorbent with the highest amount of CA produced in completely dry conditions. A study by Kharasch et al.[23] did not show any CA production with sevoflurane and partially desiccated Amsorb®. It is therefore possible that Amsorb® only produces CA when completely dehydrated. The newer product Amsorb® Plus produces no CA under any circumstances according to Struys et al.[12].

Lithiumhydroxide generates only a very small amount of CA in completely dry absorbents.

The only carbon dioxide absorbents that do not produce any CA at all with sevoflurane are LoFloSorb® and Superia®.

Based on previous studies we conclude that much higher concentrations of CA are needed than measured in this study to develop any nephrotoxic effect[24;25]. We therefore conclude that sevoflurane can be safely used with respect to CA production in low flow conditions with any of the absorbents used in these experiments. If one wishes to have no CA production at all then LoFloSorb® and Superia® are the absorbents of choice.

The case report by Fatheree et al.[26] gave rise to a new safety discussion in which the high temperature and/or degradation products of sevoflurane in partially dried Baralyme® can result in an acute respiratory distress syndrome or even explosion and fire[27;28]. Only Drägersorb 800 plus®, Medisorb® and Spherasorb® showed a discrepancy between the set dial concentration of sevoflurane versus the inhaled concentration in this study, suggesting heavy sevoflurane degradation. However, we did not measure the extreme temperatures as reported in the described case reports. Therefore, we consider it unlikely that these reactions occur in the products used in this study, and that these reactions are more related to the different composition of Baralyme®. However, because of the use of a combination of sevoflurane and nitrous oxide in this study, we cannot rule out the possibility that higher concentrations of sevoflurane without nitrous oxide would increase the absorbent temperature above a certain threshold where sodalime could ignite. Because the products Amsorb®, LoFloSorb®, Superia® and lithium hydroxide do not show the mentioned discrepancy between the dial concentration and the inhaled concentration of sevoflurane, we conclude that these products are free of severe sevoflurane degradation and are unlikely to cause fire or explosions.

When considering changing the type of absorbent, one should also consider the fact that some newer types of absorbents have a lower CO_2 absorbing capacity, as demonstrated in previous studies for Amsorb®[29;30] and LoFloSorb®[30]. However, Neumann et al. demonstrated that elimination of KOH and NaOH does not have to result in diminished carbon dioxide absorbing capacity[5], and this has also been demonstrated for Spherasorb® and Superia®[30]. The newer absorbents (not tested in this study) Drägersorb Free® and Amsorb Plus® also have comparable CO_2 absorbing capacity[31]. Therefore, we conclude that the absorbing capacity for most new absorbents free of strong bases is comparable to the absorbing capacity of sodalime. Stabernack et al.[18] demonstrated that lithium hydroxide actually has a higher carbon dioxide absorbing capacity than sodalime, but is more

corrosive than the absorbents based on calciumhydroxide. Because of this corrosive effect, and the fact that lithium hydroxide is not available in compact granules like currently used absorbents, we conclude that lithium hydroxide should first be adapted to a safe usable product before using in an delivery system for inhalation anesthetics.

Temperature measurements

Considering the fact that lower production of CA with Drägersorb 800 plus®
results in a higher temperature increase (41.7 ^{o}C) compared to the temperature increment measured with Amsorb (4.1 ^{o}C) at high levels of CA, we concluded that the temperature increases measured were not clinically relevant and a poor predictor of CA production (see also Keijzer et al. 2005)[11]. We assume that the temperature increase is related to sevoflurane degradation and not specifically to CA production.

Conclusions

In this patient model we demonstrated that different type of absorbents produce very small amounts of CA and CO or not at all. The CA concentrations are the lowest for the absorbents free of strong bases, with the exception of desiccated Amsorb®. In order of CA producing potency Amsorb®(base-free, desiccated), Drägersorb (hydrated) > Medisorb® (hydrated) >> lithiumhydroxide (base-free, desiccated), Drägersorb (dessicated), Medisorb® (dessicated), Spherasorb® (hydrated) and Spherasorb® (desiccated) produce CA. Absorbents free of strong bases, LoFloSorb®, Superia® did not produce any CA or CO in hydrated or desiccated condition.

The concentrations CA and CO found do not appear to be clinically relevant. Therefore we consider each of these carbon dioxide absorbents safe for clinical use in combination with sevoflurane, with respect to possible production of compound A and carbon monoxide. For all absorbents extreme exothermic reactions occurring with the use of a sevoflurane-nitrous oxide mixture appears to be unlikely. Temperature increase is not related to CA production.

Reference List

1. Baum J, Sitte T, Strauss JM, Forst H, Zimmerman H, Kugler B: Absorption and degradation of sevoflurane in dry soda lime. Anästhesiologie & Intensivmedizin 1998; 39: 11-6
2. Janshon GP, Dudziak R: Interactions of dry soda lime with enflurane and sevoflurane. Clinical report on two unusual anesthesias. Anaesthesist 1997; 46: 1050-3
3. Iyer RA, Baggs RB, Anders MW: Nephrotoxicity of the glutathione and cysteine S-conjugates of the sevoflurane degradation product 2-(fluoromethoxy)-1,1,3,3, 3- pentafluoro-1-propene (Compound A) in male Fischer 344 rats. J Pharmacol.Exp.Ther. 1997; 283: 1544-51
4. Kharasch ED, Thorning D, Garton K, Hankins DC, Kilty CG: Role of renal cysteine conjugate beta-lyase in the mechanism of compound A nephrotoxicity in rats. Anesthesiology 1997; 86: 160-71
5. Neumann MA, Laster MJ, Weiskopf RB, Gong DH, Dudziak R, Forster H, Eger EI: The elimination of sodium and potassium hydroxides from desiccated soda lime diminishes degradation of desflurane to carbon monoxide and sevoflurane to compound A but does not compromise carbon dioxide absorption. Anesth.Analg. 1999; 89: 768-73
6. Bouche MP, Versichelen LF, Struys MM, Van Bocxlaer JF, De Leenheer AP, Mortier EP, Rolly G: No compound a formation with Superia during minimal-flow sevoflurane anesthesia: a comparison with Sofnolime. Anesth.Analg 2002; 95: 1680-5
7. Versichelen LF, Bouche MP, Rolly G, Van Bocxlaer JF, Struys MM, De Leenheer AP, Mortier EP: Only carbon dioxide absorbents free of both NaOH and KOH do not generate compound A during in vitro closed-system sevoflurane: evaluation of five absorbents. Anesthesiology 2001; 95: 750-5
8. Holak EJ, Mei DA, Dunning MB, III, Gundamraj R, Noseir R, Zhang L, Woehlck HJ: Carbon monoxide production from sevoflurane breakdown: modeling of exposures under clinical conditions. Anesth.Analg. 2003; 96: 757-64, table
9. Laster M, Roth P, Eger EI: Fires from the interaction of anesthetics with desiccated absorbent. Anesthesia and Analgesia 2004; 99: 769-74
10. Wissing H, Kuhn I, Warnken U, Dudziak R: Carbon monoxide production from desflurane, enflurane, halothane, isoflurane, and sevoflurane with dry soda lime. Anesthesiology 2001; 95: 1205-12
11. Keijzer C, Perez RS, de Lange JJ: Carbon monoxide production from five volatile anesthetics in dry sodalime in a patient model: halothane and sevoflurane do produce carbon monoxide; temperature is a poor predictor of carbon monoxide production. BMC Anesthesiol. 2005; 5: 6
12. Struys MM, Bouche MP, Rolly G, Vandevivere YD, Dyzers D, Goeteyn W, Versichelen LF, Van Bocxlaer JF, Mortier EP: Production of compound A and carbon monoxide in circle systems: an in vitro comparison of two carbon dioxide absorbents. Anaesthesia 2004; 59: 584-9
13. Bito H, Ikeda K: Effect of total flow rate on the concentration of degradation products generated by reaction between sevoflurane and soda lime. Br.J.Anaesth. 1995; 74: 667-9
14. Bito H, Ikeda K: Long-duration, low-flow sevoflurane anesthesia using two carbon dioxide absorbents. Quantification of degradation products in the circuit. Anesthesiology 1994; 81: 340-5
15. Bito H, Ikeda K: Degradation products of sevoflurane during low-flow anaesthesia. Br.J.Anaesth. 1995; 74: 56-9
16. Higuchi H, Adachi Y, Arimura S, Kanno M, Satoh T: Compound A concentrations during low-flow sevoflurane anesthesia correlate directly with the concentration of monovalent bases in carbon dioxide absorbents. Anesth.Analg. 2000; 91: 434-9
17. Yamakage M, Yamada S, Chen X, Iwasaki S, Tsujiguchi N, Namiki A: Carbon dioxide absorbents containing potassium hydroxide produce much larger concentrations of compound A from sevoflurane in clinical practice. Anesth.Analg. 2000; 91: 220-4
18. Stabernack CR, Brown R, Laster MJ, Dudziak R, Eger EI: Absorbents differ enormously in their capacity to produce compound A and carbon monoxide. Anesth.Analg. 2000; 90: 1428-35
19. Eger EI, Ionescu P, Laster MJ, Weiskopf RB: Baralyme dehydration increases and soda lime dehydration decreases the concentration of compound A resulting from sevoflurane degradation in a standard anesthetic circuit. Anesth.Analg. 1997; 85: 892-8
20. Mchaourab A, Arain SR, Ebert TJ: Lack of degradation of sevoflurane by a new carbon dioxide absorbent in humans. Anesthesiology 2001; 94: 1007-9
21. Murray JM, Renfrew CW, Bedi A, McCrystal CB, Jones DS, Fee JP: Amsorb: a new carbon dioxide absorbent for use in anesthetic breathing systems. Anesthesiology 1999; 91: 1342-8
22. Forster H, Behne M, Warnken UH, Asskali F, Dudziak R: The use of lithium hydroxide for carbon dioxide absorption prevents formation of compound A during sevoflurane anesthesia. Anaesthesist 2000; 49: 106-12
23. Kharasch ED, Powers KM, Artru AA: Comparison of Amsorb, sodalime, and Baralyme degradation of volatile anesthetics and formation of carbon monoxide and compound a in swine in vivo. Anesthesiology 2002; 96: 173-82

24. Eger EI, Gong D, Koblin DD, Bowland T, Ionescu P, Laster MJ, Weiskopf RB: Dose-related biochemical markers of renal injury after sevoflurane versus desflurane anesthesia in volunteers. Anesth.Analg. 1997; 85: 1154-63
25. Goldberg ME, Cantillo J, Gratz I, Deal E, Vekeman D, McDougall R, Afshar M, Zafeiridis A, Larijani G: Dose of compound A, not sevoflurane, determines changes in the biochemical markers of renal injury in healthy volunteers. Anesth.Analg. 1999; 88: 437-45
26. Fatheree RA, Leighton BL: Acute respiratory distress syndrome after an exothermic baralyme-sevoflurane reaction. Anesthesiology 2004; 101: 531-3
27. Castro BA, Freedman LA, Craig WL, Lynch III C: Explosion within an anesthesia machine: Baralyme, high fresh gas flows and sevoflurane concentration. Anesthesiology 2004; 101: 537-9
28. Wu J, Previte JP, Adler E, Myers T, Ball J, Gunter JB: Spontaneous ignition, explosion, and fire with sevoflurane and barium hydroxide lime. Anesthesiology 2004; 101: 534-7
29. Higuchi H, Adachi Y, Arimura S, Kanno M, Satoh T: The carbon dioxide absorption capacity of Amsorb is half that of soda lime. Anesth.Analg. 2001; 93: 221-5
30. Knolle E, Heinze G, Gilly H: Small carbon monoxide formation in absorbents does not correlate with small carbon dioxide absorption. Anesth.Analg. 2002; 95: 650-5, table
31. Kobayashi S, Bito H, Morita K, Katoh T, Sato S: Amsorb Plus and Dragersorb Free, two new-generation carbon dioxide absorbents that produce a low compound A concentration while providing sufficient CO2 absorption capacity in simulated sevoflurane anesthesia. J.Anesth. 2004; 18: 277-81

Chapter 5

Detection of carbon monoxide production as a result of the interaction of five volatile anesthetics and desiccated sodalime with an electrochemical carbon monoxide sensor in an anesthetic circuit compared to gas chromatography

---

Christiaan Keijzer, Roberto S.G.M. Perez, Jaap J. de Lange

In revised form published in: J Clin Monit Comput. 2007 Aug; 21: 257-64

Abstract

Objectives. There is a continuing risk of production of toxic levels of carbon monoxide (CO) as a result of interaction of volatile anesthetics and desiccated carbon dioxide absorbents like soda lime. The aim of this study is to establish the reliability of detection of CO levels by an electrochemical carbon monoxide sensor, to determine if monitoring of CO with this sensor can provide an early warning sign when CO is produced inside an anesthetic circuit.

Methods. Completely desiccated sodalime was conducted through a circle anesthesia system connected to an artificial lung. For different rates of CO production, a low flow anesthesia with a oxygen/nitrous oxide mixture was maintained using five volatile anesthetics. For quantification of CO production, a portable gas chromatograph (GC) was connected to this setup, as well as a Bedfont EC40 electrochemical carbon monoxide sensor (ES) with a claimed reliable sensitivity of 0-200 parts per million (ppm) and a maximum detection range of more than 5500 ppm. To assess the agreement between the GC and ES measurements the intra class correlation coefficient (ICC) and the 95% limits of agreement were calculated. Bland and Altman scatterplots were made to visualize the difference between measurements.

Results. For concentrations up to 200 ppm, no significant differences between the GC and ES measurements were found. The ICC's between both assessments were good (0.91). For concentrations above 200 ppm the results of the two instruments differed significantly. The ES malfunctioned when exposed to sevoflurane and desiccated sodalime.

Conclusions. From these data we conclude that the ES is reliable within the range of specification. Outside the specified range the ES underestimates the actual amount of CO produced, but still provides a warning signal of CO production. When this sensor is used with sevoflurane and desiccated sodalime it's not capable of normal operation.

Introduction

There is a continuing risk of production of high concentrations of carbon monoxide (CO)[1-5] in an anesthetic circuit as a result of interaction between inhalation anesthetics and desiccated CO_2 absorbents that contain strong bases like potassium hydroxide (KOH) and sodium hydroxide (NaOH)[6;7]. There are CO_2 absorbents available that lack these strong bases and don't produce any CO when desiccated[8;9]. However, the use of these carbon dioxide absorbents is more expensive[7;10] than regular absorbents, therefore detecting CO inside the anesthesia circuit using an electrochemical could be an easier and cheaper alternative to maintain a safe patient environment, when using strong base containing CO_2 absorbents. Some electrochemical CO sensors have been studied in the presence of anesthetic gases[11;12], but only with the sensor placed in a sealed container, adding prepared CO gas mixtures that contained CO as a result of interaction between desflurane or isoflurane with a desiccated absorbent. No study has been performed with an electrochemical sensor measuring CO inside an anesthesia circle system.

Therefore, the aim of this study is to investigate the reliability of detection of CO levels by an electrochemical carbon monoxide sensor compared to gas chromatography in a patient model where carbon monoxide is generated inside an anesthesia circuit, as a result of interaction between all modern inhalation anesthetics and desiccated sodalime. We wish to determine if monitoring of CO with this sensor can provide an early warning sign of CO production inside an anesthetic circuit.

Methods and Materials

Patient model

To simulate a patient model, we used a circle anesthesia system (Cicero EM, Dräger) connected to an artificial lung (Demonstrationsthorax, Dräger).

Three sample lines were connected to the Y-piece of the circle system: one to the infrared anesthetic vapor analyzer (SAM, Marquette) sampling at 200 ml/min, one to a small lumen gas chromatography sample line connected to the gas chromatograph and one to a Datex capnograph providing a constant flow of 200 ml/min to an electrochemical carbon monoxide sensor (ES). Sampled gas from the outlet of the infrared anesthetic vapor analyzer and the capnograph was returned to the circle anesthesia system.

For the carbon monoxide production inside the circle system we used desflurane, sevoflurane, isoflurane, enflurane and halothane in combination with completely desiccated carbon dioxide absorbent Drägersorb 800 plus®, to obtain different concentrations of carbon monoxide as previously published[13].

The carbon dioxide absorbent was dried completely by using an oxygen flow of 15 l/min in glass containers until no additional weight reduction could be measured. A weight reduction of 16% was established in accordance with the producers' specifications.

Experiments

For each anesthetic, an experiment was performed in which 950 grams of dry absorbent was used. The ventilator was set in IPPV mode with a tidal volume of 600 ml, a frequency of 14 and 5 cm H_2O of PEEP. After an equilibration with 40 % oxygen and 60% nitrous oxide was established at a fresh gas flow (FGF) of 5 l/min, the GC run of 36 samples was started at t=0. After one minute, anesthetic vapor was introduced by a standard vaporizer. The dial was set until the vapor analyzer showed approximately 3.0 vol% of desflurane, 0.8 vol% sevoflurane, 0.8 vol% isoflurane, 0.6 vol% enflurane or 0.45 vol% halothane, after which the FGF was reduced to 500 ml/min. This concentration of anesthetic vapor was maintained during a 3-h experiment. All experiments were performed in duplicate to verify the reproducibility of the CO measurements. For control the same experiments were performed using fresh carbon dioxide absorbent.

Gas chromatography carbon monoxide measurements

Gas was automatically sampled every 5 minutes from the anesthetic circuit at a rate of 100 ml/min, during 10 seconds until 180 minutes. The concentrations of carbon monoxide were measured with a portable gas chromatograph (Varian Chrompack CP 2003P) with a high sensitivity thermal conductivity detector (TCD), and a Mollsieve 5A column. The reliable measurement range of this setup is 1 ppm to $1*10^6$ ppm with a margin of error of 10%. The GC was calibrated with two calibration mixtures of 210 and 981 parts per million (ppm) CO in nitrogen (Hoekloos specialty gasses, Dieren). The calibration with 981 ppm CO confirmed the linearity of the TCD. The GC was connected to a desktop PC for control of the GC and data recording, analysis and storage.

Electrochemical carbon monoxide measurements

Sampled gas from the capnograph was lead to a Bedfont EC40 electrochemical sensor. This electrochemical sensor has a range of 0-200 parts per million (ppm) and an accuracy of ±10%, the displayed concentration has a maximum value of 2000 ppm. The sensor is also equipped with a external analog signal, which we used to record the carbon monoxide concentration per second through an analog-digital converter inside the same desktop PC, as mentioned above. The ES was calibrated with a mixture of 210 and 981 ppm CO in nitrogen (Hoekloos specialty gasses, Dieren).

Statistical analysis

All statistical analyses were performed with SPSS for Windows version 12.0.

Carbon monoxide measurements from the electrochemical monitor were averaged over the same time periods of approximately five minutes as the gas chromatograph measured for comparison.

The results from the electrochemical sensor and the gas chromatograph were compared for differences using the Mann-Whitney test. The intra class correlation coefficient (ICC) and the 95% limits of agreement were used to asses the agreement between measurements. To visualize the size of difference between measurements and their distribution around zero, Bland and Altman scatterplots were made for all experiments[14]. For all analyses, the significance level was set at .05.

Results

The control experiments using fresh carbon dioxide absorbent revealed no carbon monoxide production measured by the ES or GC.

There were no differences in the carbon monoxide concentrations in the two consecutive measurements for each anesthetic with desiccated absorbent for the GC and ES (Mann-Whitney U test: $P>0.05$). Therefore the average mean CO concentrations (GC and ES) were calculated from the two experiments of each anesthetic vapor and plotted in figure 1 for halothane, in figure 2 for enflurane, in figure 3 for isoflurane and in figure 4 for desflurane. The CO curves for the GC were previously published[13].

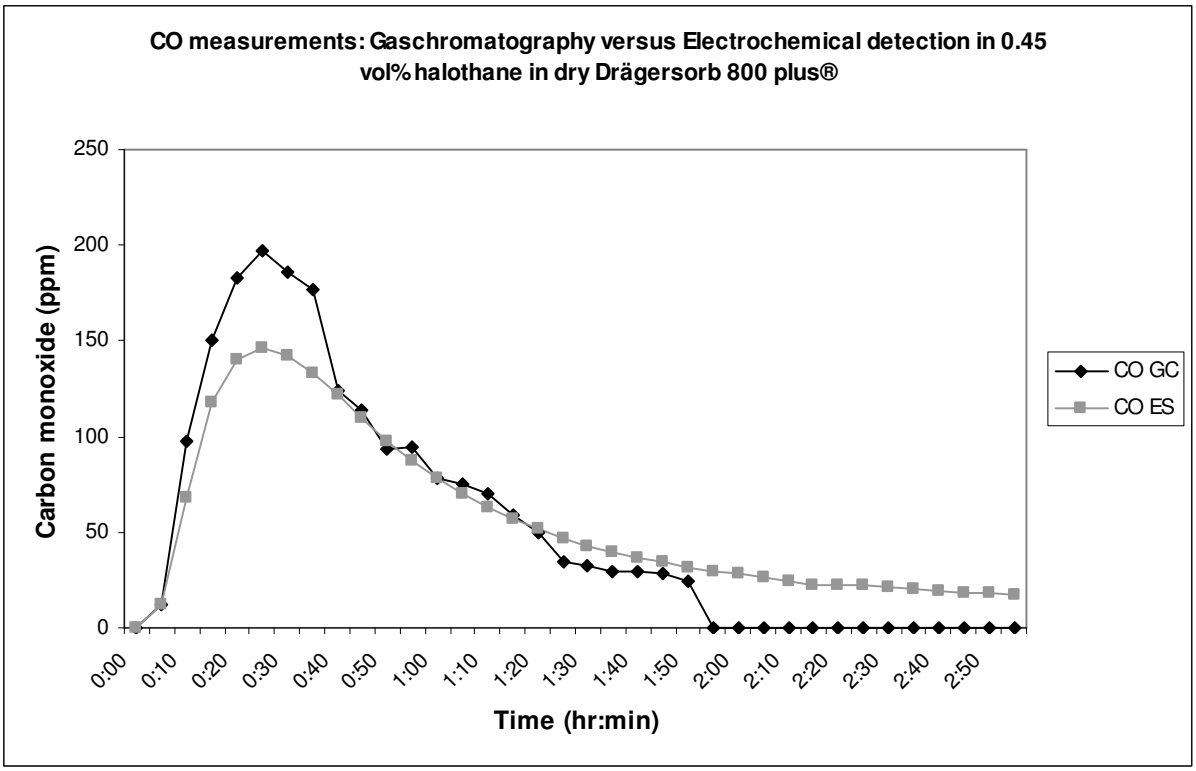


Figure 1. Carbon monoxide (CO) measurements in parts per million (ppm) by a gaschromatograph (GC) versus an electrochemical sensor (ES). Measurements are averages of two experiments performed in a circle system using 0.45 vol% halothane in completely dry Drägersorb 800 plus®.

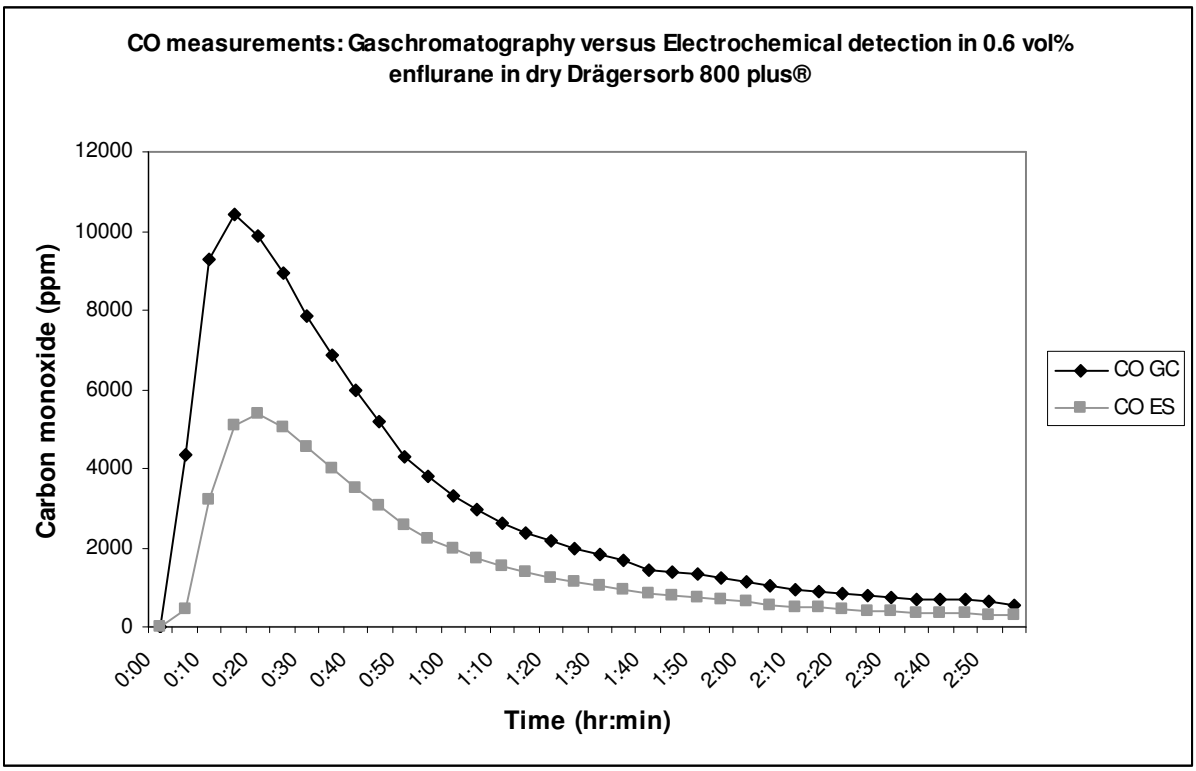


Figure 2. Carbon monoxide (CO) measurements in parts per million (ppm) by a gaschromatograph (GC) versus an electrochemical sensor (ES). Measurements are averages of two experiments performed in a circle system using 0.6 vol% enflurane in completely dry Drägersorb 800 plus®.

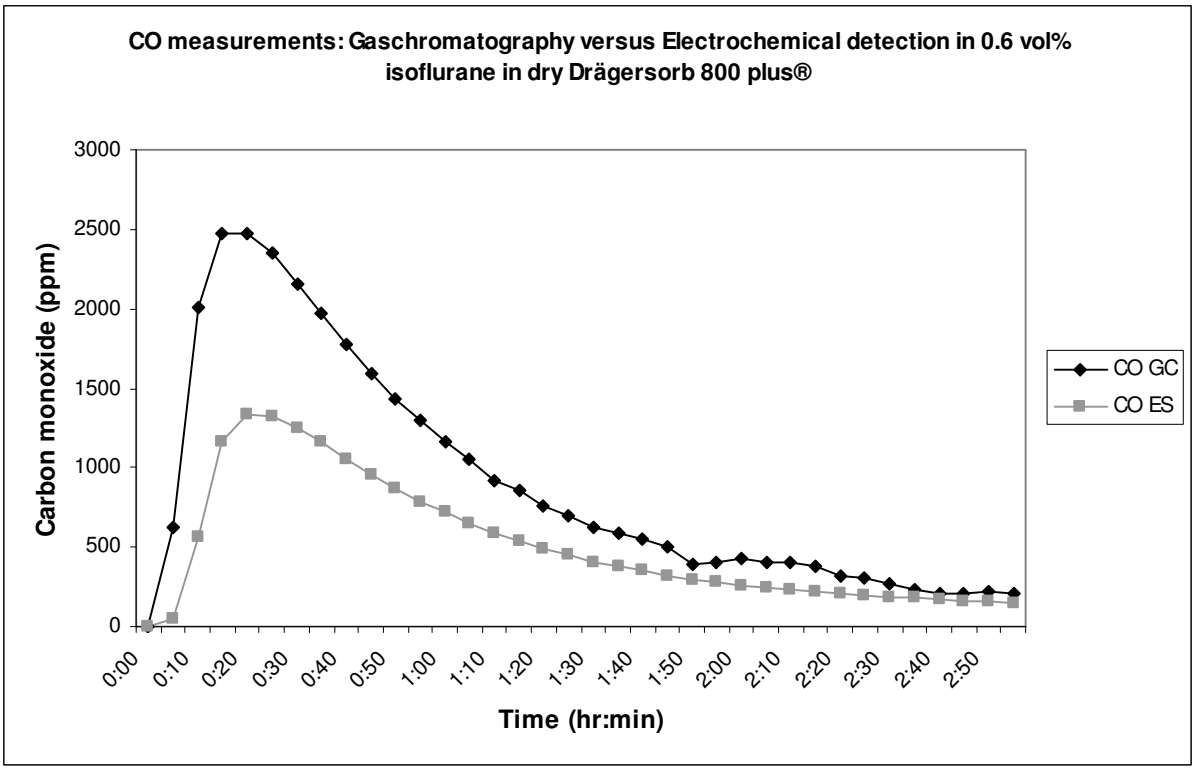


Figure 3. Carbon monoxide (CO) measurements in parts per million (ppm) by a gaschromatograph (GC) versus an electrochemical sensor (ES). Measurements are averages of two experiments performed in a circle system using 0.6 vol% isoflurane in completely dry Drägersorb 800 plus®.

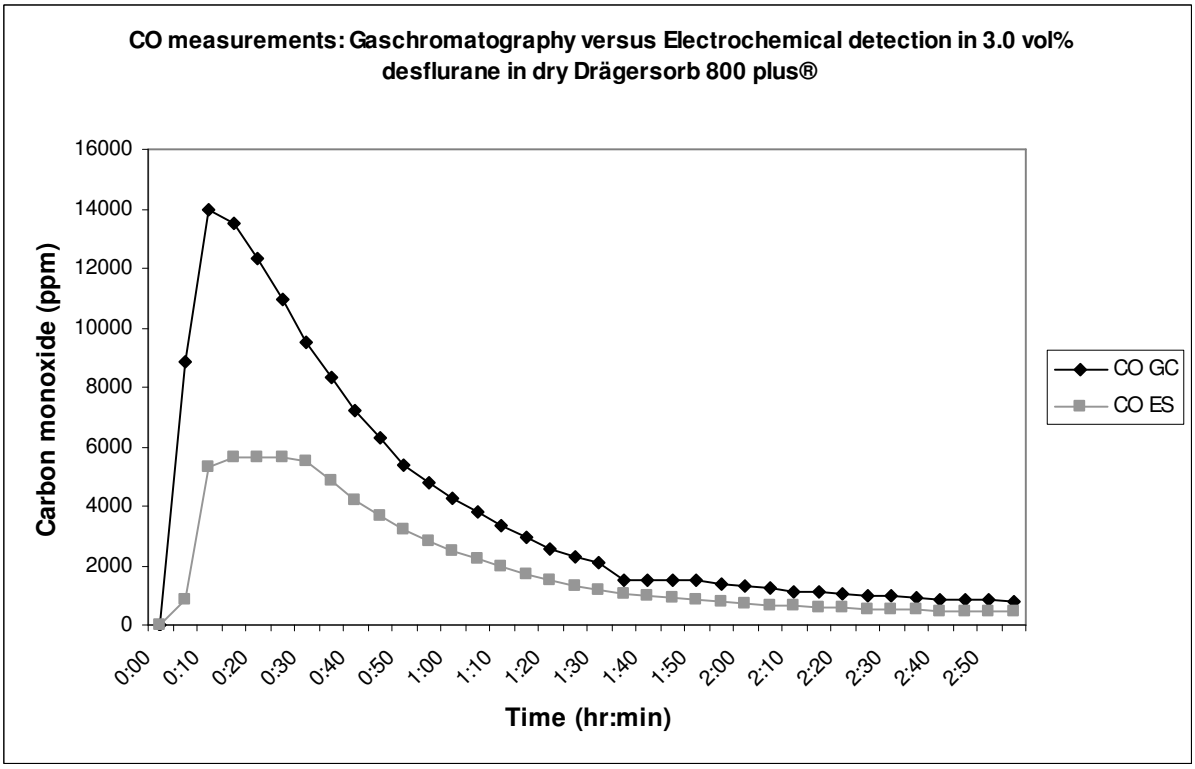


Figure 4. Carbon monoxide (CO) measurements in parts per million (ppm) by a gaschromatograph (GC) versus an electrochemical sensor (ES). Measurements are averages of two experiments performed in a circle system using 3.0 vol% desflurane in completely dry Drägersorb 800 plus®.

In the figures the two curves of the electrochemical sensor and the gas chromatograph are only comparable for the halothane experiment.

In the desflurane and enflurane experiments we noted that the upper range of the electrochemical sensor through the analog output was 5667 ppm of carbon monoxide. This explains the plateau phase in the desflurane ES-curve when the GC measures peak CO-concentrations.

The sevoflurane experiments are not depicted because of unexpected behavior of the ES during the first experiment: the display showed a rapid increase in CO concentration to the upper limit of 2000 ppm in the display and 5667 ppm through the analog output within one hour. After that the sensor output suddenly dropped to minus 2000 ppm in the display and minus 5670 ppm through the analog output. The sensor was then disconnected from the circle system and no longer used in the sevoflurane experiments with desiccated absorbent. After the disconnection the sensor was flushed with air which had no effect on the displayed CO concentration that kept indicating minus 2000 ppm for approximately twelve hours. Afterwards the sensor operated normally again and exposure to the calibration mixtures of CO in nitrogen resulted in the corresponding CO concentrations.

In table 1 all calculated data are presented.

Table 1: Carbon monoxide (CO) measurements in parts per million (ppm) by a gaschromatograph (GC) versus an electrochemical sensor (ES).

Experiment	Mean [CO] from GC	Mean [CO] from ES	GC/ES	p	ICC	95% limits
H 1	51	51	1.00	0.303	0.91	-43.8 – 43.8
H 2	56	60	0.93	0.184	0.91	-52.3 – 43.7
E 1	2914	1473	1.98	0.005	0.79	-1715.8 – 4599.0
E 2	3240	1760	1.84	0.015	0.81	-1626.4 – 4587.1
I 1	902	520	1.73	0.018	0.62	-397.1 – 1160.5
I 2	879	481	1.83	0.009	0.62	-326.0 – 1105.2
D 1	3902	1967	2.05	0.047	0.59	-2783.1 – 6653.3
D 2	4069	1986	1.98	0.004	0.57	-2899.4 – 6917.4
S 1	23	N/A	-	-	-	-
S 2	27	N/A	-	-	-	-

Legend: column 1 names the two experiments for each desiccated absorbent: H=halothane, I=isoflurane, E=enflurane, D=desflurane, S=sevoflurane. Column 2 displays the mean CO concentration measured by the GC. Column 3 displays the mean CO concentration measured by the electrochemical sensor. Column 4 displays the fraction columns 3 and 4. Column 5 displays the p value of the Mann-Whitney test comparing the results from the GC and the ES. Column 6 displays the intra class correlation value (ICC) that is calculated from a univariate analysis of variance between the results from the GC and the ES. The last column shows the 95% limits of agreement of the comparison between the GC and ES.

Mean carbon monoxide concentrations in the halothane experiments correspond with a GC/ES fraction of 0.93 to 1.00. No significant differences were found for the halothane experiments between the GC and ES data, and the high ICC between both assessments is good. The other experiments demonstrate significant differences between GC and ES data and moderate ICC's, with a GC/ES fraction of 1.73 to 2.05. The 95% limits of agreements show that the difference between the GC and ES is maximally 100 ppm for the halothane experiments, with a discrepancy being equally likely in both directions. For the isoflurane and desflurane experiments, the difference between both instruments maximally differs respectively 1560 and 9825 ppm, whereby the ES measurements tend to underestimate the amount of CO produced. The Bland and Altman scatter plots (figures 5-12) also depict the distribution of the differences around zero between experiments, and also show a relationship between the amount of CO production and the size of the observed difference between both instruments for all experiments.

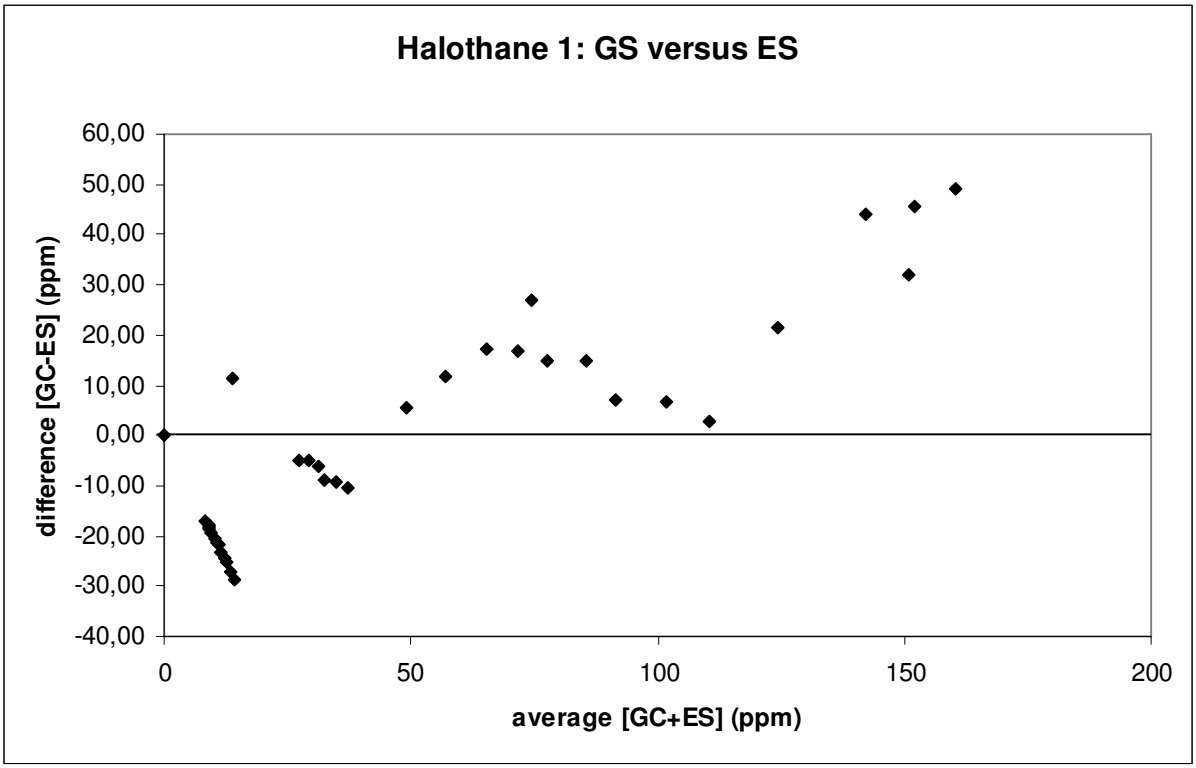


Figure 5. Scatterplot of difference between CO concentrations of the GC and ES measurements against the mean concentrations of GC and ES in the first halothane experiment. Concentrations in parts per million (ppm).

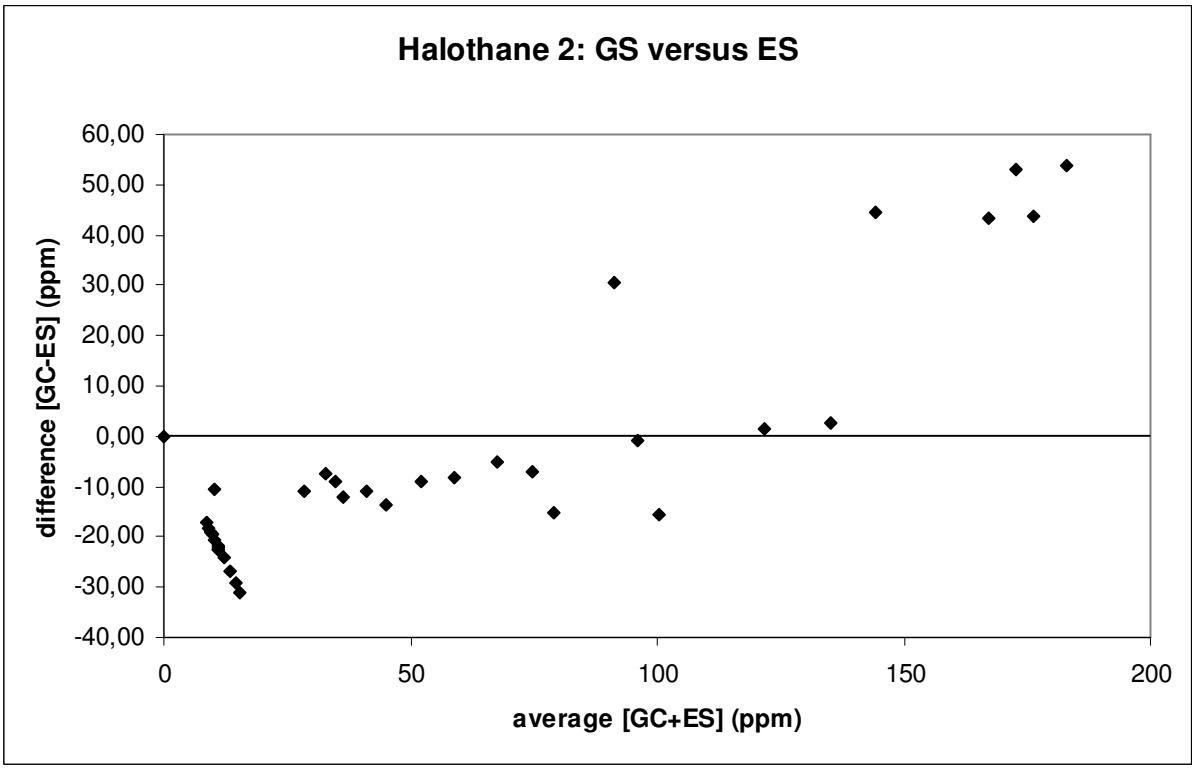


Figure 6. Scatterplot of difference between CO concentrations of the GC and ES measurements against the mean concentrations of GC and ES in the second halothane experiment. Concentrations in parts per million (ppm).

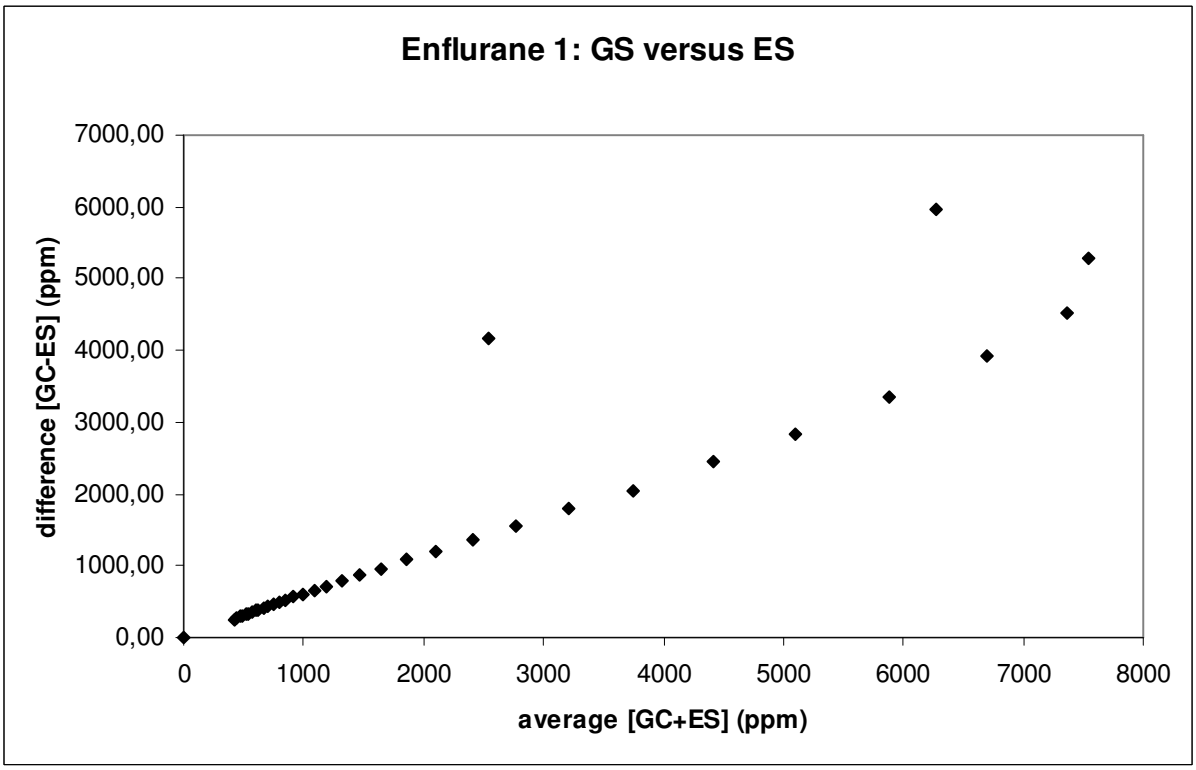


Figure 7. Scatterplot of difference between CO concentrations of the GC and ES measurements against the mean concentrations of GC and ES in the first enflurane experiment. Concentrations in parts per million (ppm).

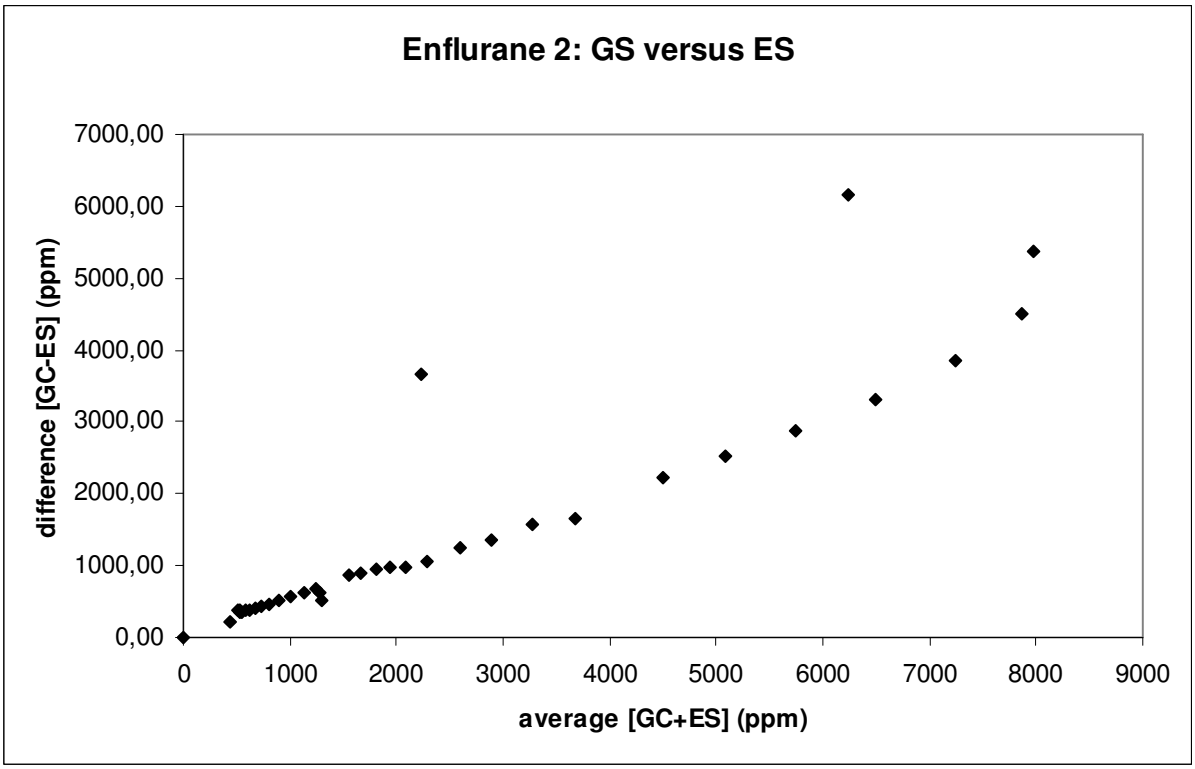


Figure 8. Scatterplot of difference between CO concentrations of the GC and ES measurements against the mean concentrations of GC and ES in the second enflurane experiment. Concentrations in parts per million (ppm).

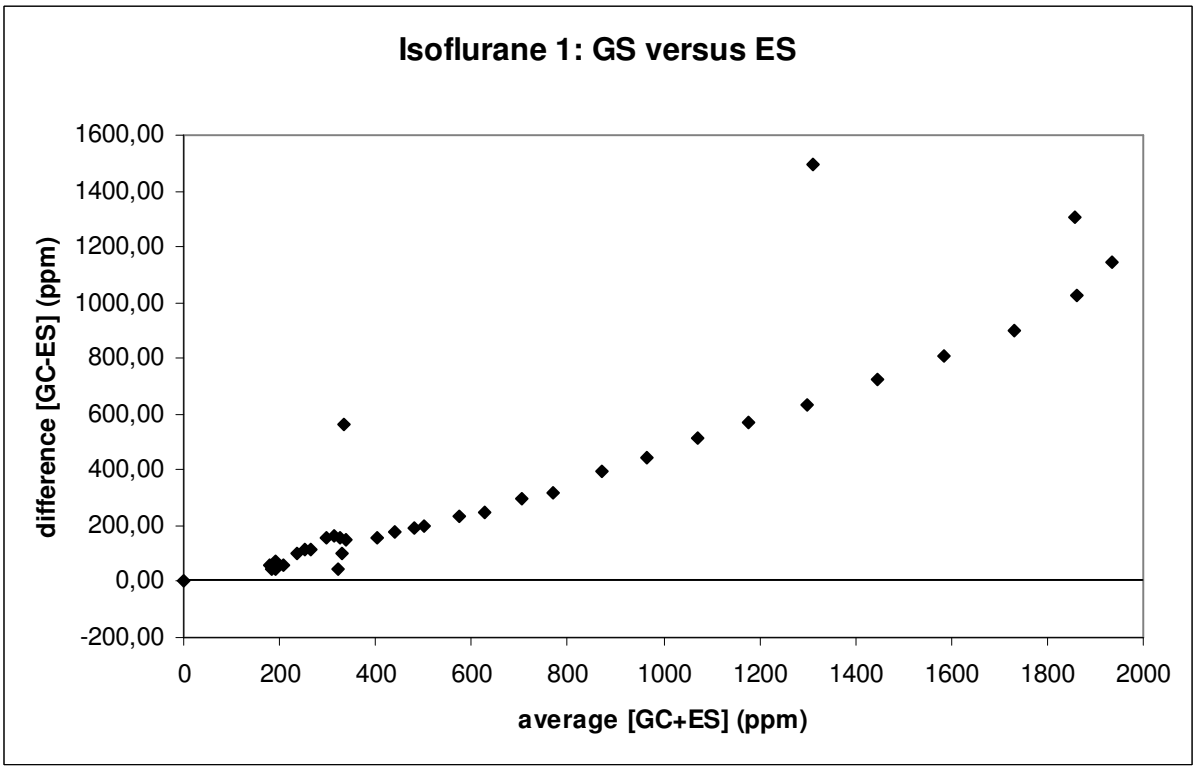


Figure 9. Scatterplot of difference between CO concentrations of the GC and ES measurements against the mean concentrations of GC and ES in the first isoflurane experiment. Concentrations in parts per million (ppm).

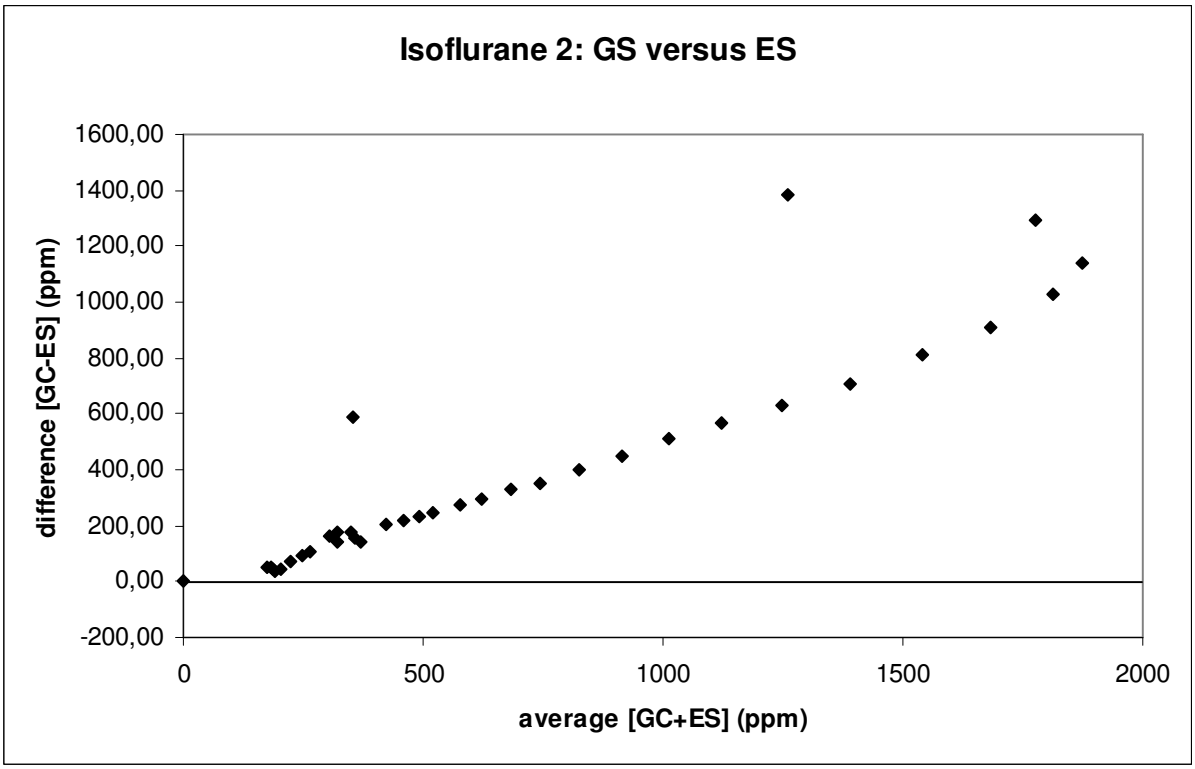


Figure 10. Scatterplot of difference between CO concentrations of the GC and ES measurements against the mean concentrations of GC and ES in the second isoflurane experiment. Concentrations in parts per million (ppm).

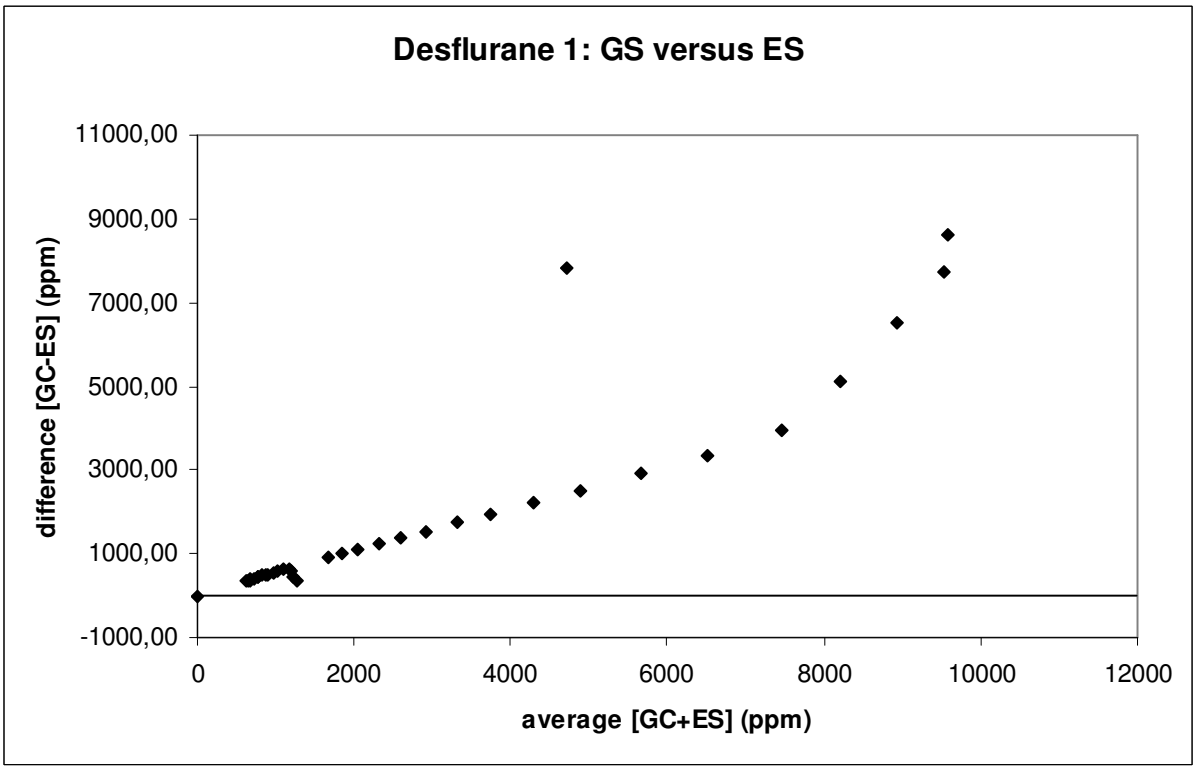


Figure 11. Scatterplot of difference between CO concentrations of the GC and ES measurements against the mean concentrations of GC and ES in the first desflurane experiment. Concentrations in parts per million (ppm).

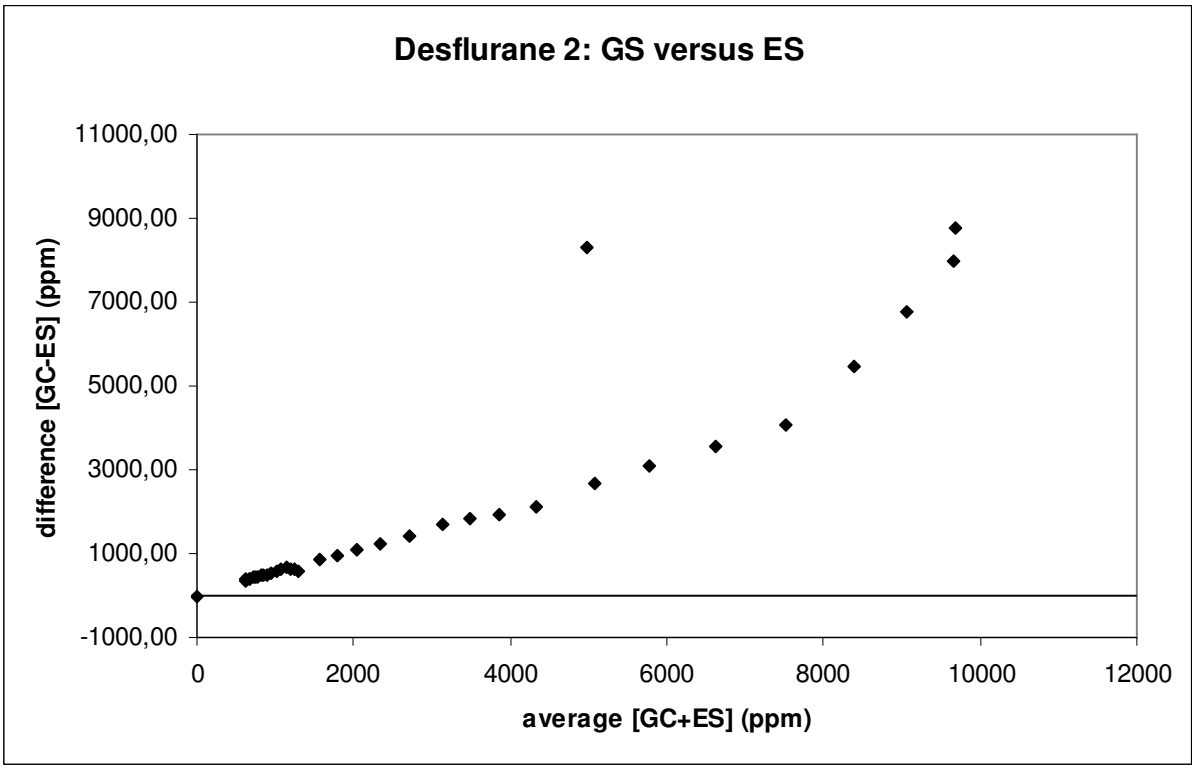


Figure 12. Scatterplot of difference between CO concentrations of the GC and ES measurements against the mean concentrations of GC and ES in the second desflurane experiment. Concentrations in parts per million (ppm).

Discussion

In this study we demonstrated that the Bedfont EC-40 electrochemical CO sensor can detect low concentrations of CO up to 200 ppm comparable to the CO concentrations measured by the GC in an anesthetic circuit. Previous studies[11;12] demonstrated accurate reliability of different brands of electrochemical sensors with carbon monoxide production from isoflurane or desflurane and desiccated carbon dioxide absorbents within the specified range of the sensors. From this study we can confirm that also this electrochemical sensor measures comparable to a GC within the specified range for the experiments with halothane.

This cannot be concluded for CO production from sevoflurane in combination with desiccated sodalime, whereby the sensor displayed negative concentrations of CO while the actual (GC) carbon monoxide concentrations were within the specified range of the sensor. In these experiments we also noticed a high degree of sevoflurane degradation because of the discrepancy between the

dial setting of the vaporizer and the measured sevoflurane concentrations in the circle system as previously reported[13]. When sevoflurane degradation occurs in the presence of this sensor, the display will show increasing concentrations of CO before it shuts down and is therefore providing a warning signal of sevoflurane degradation as result of absorbent desiccation. Funk et al.[15] demonstrated that when sevoflurane degrades in desiccated sodalime, also compound A to E, methanol, formaldehyde, fluoride and formic acid are produced. From the producer of the electrochemical sensor we know that the reaction mechanism of the sensing electrode is represented by the equation: $CO + H_2O = CO_2 + 2H^+ + 2e^-$ and that this mechanism can easily be disturbed in the presence of formaldehyde, formic acid or methanol. Because this sensor also contains an inboard filter to remove acid gases and alcohols we think that most likely the produced formaldehyde is responsible for the inaccuracy of the sensor in this experiment.

Outside the specified range of this ES the measured CO concentration are below the actual numbers measured by the GC for the other experiments. This applies to the experiments with enflurane, isoflurane and desflurane in combination with desiccated sodalime.

Still this sensor can provide an early warning signal of CO production but with a highly underestimated concentration displayed. For example: in the experiments with desflurane the GC measured in the first sample after five minutes CO concentrations of approximately 9000 ppm. The ES however started to measure concentrations of 100 ppm after two minutes, that rapidly increased to 700 ppm after three minutes. On the other hand after five minutes the ES measured approximately 800 pmm of CO which is about 10% of the real measured concentration by the GC in the first sample. When the alarm of the ES is set at 200 ppm, this sensor would give an early warning signal of CO production in this situation after two to three minutes before the GC returns it's first results. One should take into account though, that the displayed concentration of CO is highly underestimated with this high concentration. Nevertheless the patient would not be in danger when exposed to these CO concentrations[16] in this short time period, under the condition that the

absorbent would be changed immediately after the first warning of CO production. When comparing the ES as index test to the GC as reference test the sensitivity and specificity for desflurane and enflurane is 100% and for isoflurane respectively 97% and 100%. This with a positive test defined as a CO detection above 200 ppm and a negative test as a CO detection below 200 ppm, calculated for all samples measured by the GC and ES for the experiments with these vapor anesthetics and desiccated sodalime.

Regarding the cost effectiveness of implementing an electrochemical CO sensor we calculated the extra cost using the strong base free Drägersorb free® for the last two years instead of Drägersorb 800 plus® for the Netherlands cancer institute – Antoni van Leeuwenhoek hospital at approximately € 2200,- per year for five operating theatres. These extra costs are a result of the higher pricing of the strong base free absorbent and the lower carbon dioxide absorbent capacity of these type of absorbents. A Bedfont electrochemical sensor device costs approximately € 1000,- with an electrochemical sensor cell lifetime of three years, a replacement cell costs approximately € 300,-. The extra costs of the strong base free absorbent during a period of three years would be € 6600,- while the purchase of five electrochemical sensor devices would cost € 5000,-. The three years thereafter the extra costs of the strong base free absorbents would be still € 6600,- while the purchase of five replacement electrochemical sensors would cost € 1500,-. Based on these figures the relatively cost reduction per theatre would be approximately € 300,- yearly for the first three years and about € 1300,- for the following years when implementing this electrochemical sensor in stead of replacing the absorbent to a strong base free type.

Conclusions

From this study we conclude that this electrochemical sensor can provide an early warning sign of CO production when using a strong base containing carbon dioxide absorbent and vapor anesthetics in an anesthesia circle system. However, above the specified range 200 ppm the sensor becomes inaccurate resulting in an highly underestimation of the actual CO concentrations, still indicating a CO production that requires an immediate change of the carbon dioxide absorbent. When sevoflurane is degraded in desiccated sodalime this sensor is not capable of normal operation and will display high (incorrect) concentrations of CO within half an hour. These high CO concentrations are still a warning signal for desiccation of the absorbent and should also lead to an immediate change of absorbent.

Implementing this electrochemical sensor instead of replacing the strong base containing absorbent to a strong base free type will lead to a slight cost reduction over three to six years.

Reference List

1. Moon R, Meyer A, Scott D, Fox E, Millington D, Norwood D: Intraoperative carbon monoxide toxicity. Anesthesiology 1990; 73: A1089
2. Moon R, Ingram C, Brunner E, Meyer A: Spontaneous generation of carbon monoxide within anesthetic circuits. Anesthesiology 1991; 75: A873
3. Lentz R: CO poisoning during anesthesia poses puzzles. APSF Newsletter 1994; 9: 13-4
4. Berry PD, Sessler DI, Larson MD: Severe carbon monoxide poisoning during desflurane anesthesia. Anesthesiology 1999; 90: 613-6
5. Fatheree RA, Leighton BL: Acute respiratory distress syndrome after an exothermic baralyme-sevoflurane reaction. Anesthesiology 2004; 101: 531-3
6. Neumann MA, Laster MJ, Weiskopf RB, Gong DH, Dudziak R, Forster H, Eger EI: The elimination of sodium and potassium hydroxides from desiccated soda lime diminishes degradation of desflurane to carbon monoxide and sevoflurane to compound A but does not compromise carbon dioxide absorption. Anesth.Analg. 1999; 89: 768-73
7. Stabernack CR, Brown R, Laster MJ, Dudziak R, Eger EI: Absorbents differ enormously in their capacity to produce compound A and carbon monoxide. Anesth.Analg. 2000; 90: 1428-35
8. Murray JM, Renfrew CW, Bedi A, McCrystal CB, Jones DS, Fee JP: Amsorb: a new carbon dioxide absorbent for use in anesthetic breathing systems. Anesthesiology 1999; 91: 1342-8
9. Struys MM, Bouche MP, Rolly G, Vandevivere YD, Dyzers D, Goeteyn W, Versichelen LF, Van Bocxlaer JF, Mortier EP: Production of compound A and carbon monoxide in circle systems: an in vitro comparison of two carbon dioxide absorbents. Anaesthesia 2004; 59: 584-9
10. Higuchi H, Adachi Y, Arimura S, Kanno M, Satoh T: The carbon dioxide absorption capacity of Amsorb is half that of soda lime. Anesth.Analg. 2001; 93: 221-5
11. Dunning M, III, Woehlck HJ: Performance of an electrochemical carbon monoxide monitor in the presence of anesthetic gases. J.Clin.Monit. 1997; 13: 357-62
12. Bermudez JA: Investigation of electrochemical carbon monoxide sensor monitoring of anesthetic gas mixtures. Anesthesiology 2003; 99: 1233-5
13. Keijzer C, Perez RS, de Lange JJ: Carbon monoxide production from five volatile anesthetics in dry sodalime in a patient model: halothane and sevoflurane do produce carbon monoxide; temperature is a poor predictor of carbon monoxide production. BMC Anesthesiol. 2005; 5: 6
14. Altman D: Practical statistics for medical research. Chapman & Hall, 1999,
15. Funk W, Gruber M, Wild K, Hobbhahn J: Dry soda lime markedly degrades sevoflurane during simulated inhalation induction. Br.J.Anaesth. 1999; 82: 193-8
16. Altman C: AANA journal course: update for nurse anesthetists--carbon monoxide poisoning: role of the anesthesia machine's carbon dioxide absorption system. AANA.J. 1996; 64: 41-7

Chapter 6

Carbon monoxide and Compound A measurements with desflurane and sevoflurane anesthesia in humans: an observational study

---

Christiaan Keijzer, Roberto S.G.M. Perez, Jaap J. de Lange

Submitted for publication

Abstract

Background: All modern vapor anesthetics are capable of carbon monoxide (CO) production as a result of interaction with desiccated strong base containing carbon dioxide absorbents. In desiccated absorbents, desflurane produces the highest concentrations of CO. Sevoflurane is known to produce the nephrotoxic compound A (CA) independent of the water content of the carbon dioxide absorbent. The purpose of this study is to register the average CO concentrations in forty patients receiving desflurane or sevoflurane anesthesia after implementation of a safety protocol adapted from Woehlck et al., developed to prevent desiccation of the strong base containing absorbent Drägersorb 800 Plus® while still maintaining the possibility of flushing the ventilating circuits of the anesthesia machines with a flow of air.

Methods: In 40 patients a low-flow anesthesia was maintained using an oxygen/air mixture with either sevoflurane or desflurane in combination with the CO_2 absorbent Drägersorb 800 plus®. CO and CA production was measured in the inspiratory limb of the anesthesia machine using a portable gas chromatograph, with a sampling frequency of 12 samples per hour.

Results: No carbon monoxide was measured in any of the desflurane or sevoflurane anesthesia's. The mean concentration of CA for sevoflurane anesthesia's was 17.1 ± 5.5 parts per million.

Conclusion: With the introduction of a safety protocol no carbon monoxide was measured in desflurane or sevoflurane anesthesia's. Compound A is almost continuously detected in sevoflurane anesthesia's in clinically insignificant concentrations. Implementation of a simple safety protocol may prevent desiccation of the absorbent and subsequently reduce the risk of carbon monoxide intoxication.

Introduction

For all modern vapor anesthetics, it is known that they are capable of carbon monoxide (CO) production as a result of interaction with desiccated carbon dioxide absorbents containing strong bases[1;2]. Besides CO production, sevoflurane also produces other degradation products[3;4], the most important being fluoromethyl-2,2-difluoro-1-(trifluoromethyl)vinyl ether (Compound A). Compound A has proven to be nephrotoxic in rats[5;6]. For CO production to occur, the water content of the strong base containing carbon dioxide absorbent sodalime needs to be less than 4,8%[1]. Compound A (CA) is also generated in combination with normally hydrated carbon dioxide absorbents[7]. In a previous study we registered very high concentrations of CO from 3,0 vol% desflurane using the strong base containing absorbent Drägersorb 800 plus® when completely desiccated. Other vapor anesthetics produced less CO in decreasing concentrations from enflurane >> isoflurane >> halothane > sevoflurane[8]. In another study, we published the maximum concentrations of CA for sevoflurane in combination with seven different types of absorbents in fresh and desiccated condition[9]. In this study we demonstrated that only low concentrations of CA were produced, which were not clinically relevant.

With the introduction of desflurane as volatile anesthetic in this hospital, a safety protocol as described by Woehlck et al.[10] was implemented in our institution to reduce this risk of carbon monoxide production when using the strong base containing carbon dioxide absorber Drägersorb 800 plus®. We adapted this protocol to prevent desiccation of the carbon dioxide absorbents, while still maintain the possibility of flushing the ventilating circuits of the anesthesia machines with a flow of air:

1) The anesthesia nurses were instructed to close the oxygen flow of the anesthesia machine after the operating program was finished.

2) An air flow could be used to flush the ventilating circuits of the anesthesia machine, limited in duration up to one hour.
3) When at the start of the day a fresh gas flow of oxygen was detected, the absorbent should be changed immediately.

In order to gain insight in regular clinical practice after implementing this safety protocol, we wanted to compare a potential strong CO producing volatile anesthetic (desflurane) with a weak CO producing anesthetic (sevoflurane), and simultaneously investigate if the average CA concentrations in sevoflurane anesthesia's are comparable to the low ranges found in our laboratory study. Therefore, the aim of this observational study is to register the average CO and CA concentrations in a group of patients receiving desflurane or sevoflurane anesthesia.

Methods

This study was approved by the Committee on Human Research of the VU University Medical Center, where this study was performed. The committee took the view that informed consent was not necessary and should not be obtained considering the fact that a normal anesthesia procedure with an additional non-invasive measurement was performed. The study group included 40 non-smoking patients categorized as American Society of Anesthesiologists physical status class 1 to 3, who were scheduled for a surgical procedure that would last at least ninety minutes. Patients younger than 18 years of age or suffering from terminal renal failure were excluded. All patients of one scheduled surgery program day, were randomly assigned with randomization envelopes, to receive either desflurane or sevoflurane anesthesia. Forty patients were included in twenty one surgery program days. The anesthesia machine used was a Dräger Cicero EM® circle system. Patients were premedicated with 1000 mg paracetamol one hour before anesthesia was induced. After administration of 100% oxygen for several minutes, anesthesia was induced by 3 μg/kg

fentanyl , 1.5 to 2.5 mg/kg propofol and 0.6 mg/kg rocuronium. Following tracheal intubation, the fresh gas flow rate (FGF) was set to 5 l/min and either desflurane or sevoflurane was introduced by a standard vaporizer. When a concentration of 4.0 vol% desflurane or 2.0 vol% sevoflurane was reached, the FGF was reduced at the discretion of the anesthesiologist to a minimum of 500 and a maximum of 1000 ml/min. The ratio of the oxygen to air flow rates was adjusted to maintain the oxygen concentration in the inspiratory limb above 30%. The anesthetic concentration was adjusted to maintain systolic blood pressure within 20% (±) of baseline. If necessary, extra fentanyl was administered. The lungs were ventilated mechanically with a tidal volume of 8 ml/kg, with the ventilatory rate adjusted to maintain an end-tidal carbon dioxide concentration of 30-40 mmHg.

Compound A and carbon monoxide measurements

During anesthesia, gas was automatically sampled every 5 minutes from the inspiratory limb of the anesthetic circuit at a rate of 100 ml/min during 10 seconds for measuring the concentrations of compound A and carbon monoxide with a portable gas chromatograph (Varian Chrompack CP 2003P). The gas chromatograph (GC) was equipped with a high sensitivity thermal conductivity detector (TCD) and a Poraplot Q column for isolating CA and a Mollsieve 5A column for isolating CO. The reliability range of detection of this setup is 1 ppm to $1*10^6$ ppm with a margin of error of 10%. The GC was calibrated with a calibration mixture of 12 parts per million (ppm) CA in nitrogen (Scott specialty gasses, The Netherlands) derived from three millilitres of 99,6% pure CA (Baxter Pharmaceutical Products Inc., New Providence, NJ). Calibration for CO was done with a mixture of 210 ppm CO in nitrogen (Hoekloos specialty gasses, Dieren), a second mixture of 981 ppm CO in nitrogen confirmed the linearity of the TCD. The gas chromatograph (GC) was connected to a desktop PC for control of the GC and data recording, analysis and storage.

Analysis of data

Analyzes were performed with SPSS for Windows version 12.0. Measured values are expressed as means ± standard deviation. Distribution of sex, age and anesthesia time for the desflurane and sevoflurane group were compared with a F-test. For all analyzes the significance level was set at 5%.

Results

There were no significant differences in distribution of sex, age and anesthesia time for the two groups (table 1).

	Desflurane	**Sevoflurane**	**p**
Number of patients	20	20	-
Male / Female	9 / 11	8 / 12	0.47
Age (yr)	60.2 ± 15.2	54.6 ± 18.1	0.22
Duration of anesthesia	2h21m ± 28m	2h18m ± 30m	0.42

Table 1: Number of patients, distribution of sex, mean age (yr=years) and anesthesia duration (h=hours,m=minutes) in both groups. Values for age and duration of anesthesia are mean ± SD.
P-value in the 3rd column.

For both groups, no CO was measured in any of the experiments. CA was only detected in the sevoflurane group.

The mean concentration of CA for all patients receiving sevoflurane anesthesia was 17.1 parts per million (ppm) with a standard deviation of 5.5 ppm. the minimum concentration of CA was 0.0 ppm and the maximum concentration 37.5 ppm. Several sevoflurane anesthesia's had a minimum concentration of 0.0 ppm of CA at the start of the experiment while most sevoflurane anesthesia's started with a certain concentration of CA in the inspiratory limb. For all sevoflurane anesthesia's, an increase in CA concentration was measured following the FGF reduction 5-10 minutes after the start of the anesthesia. Subsequently, the CA concentration seemed to stabilize around the

maximum value for the experiment. The CA concentrations for all sevoflurane anesthesia's are displayed in table 2.

Anesthesia nr.	Mean [CA]	Minimum [CA]	Maximum [CA]
1	16.3 ± 4.4	1.5	23.1
2	20.9 ± 6.7	0.0	27.4
3	18.0 ± 0.7	16.3	20.0
4	14.0 ± 4.9	0.0	17.9
5	13.6 ± 3.1	4.7	17.1
6	14.8 ± 3.1	1.1	19.6
7	15.9 ± 2.2	12.9	19.0
8	18.4 ± 3.2	9.0	23.9
9	18.2 ± 3.9	0.0	22.1
10	16.1 ± 3.0	7.8	20.0
11	21.2 ± 5.3	8.3	29.7
12	21.3 ± 3.0	17.4	30.3
13	15.1 ± 3.6	0.3	20.7
14	13.4 ± 1.9	9.8	15.8
15	14.7 ± 0.6	13.0	15.3
16	28.8 ± 7.3	0.0	37.5
17	10.9 ± 1.4	6.2	14.6
18	13.7 ± 2.7	5.1	16.2
19	17.0 ± 5.3	3.7	22.8
20	17.9 ± 5.3	4.6	23.6

Table 2: Mean, minimum and maximum compound A (CA) concentrations from all sevoflurane anesthesia's. Column 1 states the anesthesia number, column 2 the mean CA concentration ± SD for that experiment. Column 3 and 4 display respectively the minimum and maximum CA concentration. Concentrations in parts per million (ppm)

Discussion

In this study we demonstrated that carbon monoxide is not produced by desflurane or sevoflurane in controlled clinical situations. Small amounts of Compound A are only produced by sevoflurane.

In the desflurane anesthesia's, we did not measure any CO in the inspiratory limb, although we would expect at least a few ppm of carbon monoxide from the patients metabolism[11], when no CO is produced inside the carbon dioxide absorbent. Possibly, these small concentrations of CO did not reach the inspiratory limb because of the small spill of gas in the semi-closed anesthesia system we used. The fact that no CO was produced in these anesthesia's means that the water content of the

absorbent was always above 4,8%[1]. This demonstrates the rareness of complete desiccation of the absorbent in this clinical situation. This prevention of complete desiccation is probably due to the fact that the anesthesia nurses were instructed to use the safety protocol as described in the introduction. In this protocol, a flow of air is used when flushing the ventilating circuits of the anesthesia machines after surgery is necessary. A flow of air contains 0.03% of carbon dioxide that generates water when it reacts with the calcium hydroxide inside the absorbent, therefore preventing the absorbent from desiccating. Furthermore, a fresh gas flow of oxygen was never found in the anesthesia machine at the start of each study day, and the absorber did not have to be changed at any time. A limitation of this study is that this protocol was not tested against performance of anesthesia's without a safety protocol while using this strong base containing absorbent in combination with desflurane. For ethical reasons this option was not considered.

In the sevoflurane anesthesia's, we measured an increase of the measured CA concentration after the FGF was reduced from a flow of 5 l/min to a flow of 500 – 1000 ml/min. This is in accordance with other studies[12-15] which demonstrated that a low flow will increase the amount of CA measured inside the circle system. This variation of FGF in these sevoflurane anesthesia's may explain the differences in the mean CA concentrations varying between 13.4 and 28.8 ppm.

The CA concentrations measured in the present study are higher than in our previous laboratory study[9]. This is most probably due to the fact that we used 1.5 to 2.5 vol% sevoflurane in this study in stead of the 0.8 vol% sevoflurane with 60% nitrous oxide in the laboratory study. The CA concentrations found in this study are comparable with concentrations found in other studies[12;16] using the same concentrations of sevoflurane during low-flow anesthesia. In the first samples of four anesthesia's (three of which were the first anesthesia of the day) no CA was measured. We assume that this lack of CA production was due to flushing of the anesthesia machine with air overnight or between anesthesia's. For the majority of anesthesia's, small amounts of CA were

measured in the first sample, which were probably the result of CA formation from the previous anesthesia.

Although transient nephrotoxicity was demonstrated by Eger et al.[17] and Goldberg et al.[18] with respectively 80-160 ppm/h and 240 ppm of CA exposure in humans, the majority of publications demonstrate no nephrotoxicity in humans with the use of sevoflurane in combination with any kind of absorbent in a clinical setting[19-21]. The results of this study, together with the results from our laboratory study[9], confirm these observations.

Conclusions

No carbon monoxide was measured during desflurane or sevoflurane anesthesia's. This was possibly attributable to the use of a safety protocol, whereby the flow of air used to flush the ventilating circuits of the anesthesia machine does not desiccate the carbon dioxide absorbent. Compound A is almost continuously measured in sevoflurane anesthesia's in clinically insignificant concentrations.

Reference List

1. Fang ZX, Eger EI, Laster MJ, Chortkoff BS, Kandel L, Ionescu P: Carbon monoxide production from degradation of desflurane, enflurane, isoflurane, halothane, and sevoflurane by soda lime and Baralyme. Anesth.Analg. 1995; 80: 1187-93
2. Stabernack CR, Brown R, Laster MJ, Dudziak R, Eger EI: Absorbents differ enormously in their capacity to produce compound A and carbon monoxide. Anesth.Analg. 2000; 90: 1428-35
3. Baum J, Sitte T, Strauss JM, Forst H, Zimmerman H, Kugler B: Absorption and degradation of sevoflurane in dry soda lime. Anästhesiologie & Intensivmedizin 1998; 39: 11-6
4. Brown B, Jr.: Sevoflurane: introduction and overview. Anesth.Analg. 1995; 81: S1-S3
5. Iyer RA, Baggs RB, Anders MW: Nephrotoxicity of the glutathione and cysteine S-conjugates of the sevoflurane degradation product 2-(fluoromethoxy)-1,1,3,3, 3- pentafluoro-1-propene (Compound A) in male Fischer 344 rats. J Pharmacol.Exp.Ther. 1997; 283: 1544-51
6. Kharasch ED, Thorning D, Garton K, Hankins DC, Kilty CG: Role of renal cysteine conjugate beta-lyase in the mechanism of compound A nephrotoxicity in rats. Anesthesiology 1997; 86: 160-71
7. Eger EI, Ionescu P, Laster MJ, Weiskopf RB: Baralyme dehydration increases and soda lime dehydration decreases the concentration of compound A resulting from sevoflurane degradation in a standard anesthetic circuit. Anesth.Analg. 1997; 85: 892-8
8. Keijzer C, Perez RS, de Lange JJ: Carbon monoxide production from five volatile anesthetics in dry sodalime in a patient model: halothane and sevoflurane do produce carbon monoxide; temperature is a poor predictor of carbon monoxide production. BMC Anesthesiol. 2005; 5: 6
9. Keijzer C, Perez RS, de Lange JJ: Compound A and carbon monoxide production from sevoflurane and seven different types of carbon dioxide absorbent in a patient model. Acta Anaesthesiol Scand 2007; 51: 31-7
10. Woehlck HJ, Dunning M, III, Connolly LA: Reduction in the incidence of carbon monoxide exposures in humans undergoing general anesthesia. Anesthesiology 1997; 87: 228-34
11. Coburn RF: Endogenous carbon monoxide production. N.Engl.J.Med. 1970; 282: 207-9
12. Bito H, Ikeda K: Effect of total flow rate on the concentration of degradation products generated by reaction between sevoflurane and soda lime. Br.J.Anaesth. 1995; 74: 667-9
13. Bito H, Ikeuchi Y, Ikeda K: Effects of low-flow sevoflurane anesthesia on renal function: comparison with high-flow sevoflurane anesthesia and low-flow isoflurane anesthesia. Anesthesiology 1997; 86: 1231-7
14. Fang ZX, Eger EI: Factors affecting the concentration of compound A resulting from the degradation of sevoflurane by soda lime and Baralyme in a standard anesthetic circuit. Anesth.Analg. 1995; 81: 564-8
15. Baxter AD: Low and minimal flow inhalational anaesthesia. Can.J.Anaesth. 1997; 44: 643-52
16. Bito H, Ikeda K: Closed-circuit anesthesia with sevoflurane in humans. Effects on renal and hepatic function and concentrations of breakdown products with soda lime in the circuit. Anesthesiology 1994; 80: 71-6
17. Eger EI, Gong D, Koblin DD, Bowland T, Ionescu P, Laster MJ, Weiskopf RB: Dose-related biochemical markers of renal injury after sevoflurane versus desflurane anesthesia in volunteers. Anesth.Analg. 1997; 85: 1154-63
18. Goldberg ME, Cantillo J, Gratz I, Deal E, Vekeman D, McDougall R, Afshar M, Zafeiridis A, Larijani G: Dose of compound A, not sevoflurane, determines changes in the biochemical markers of renal injury in healthy volunteers. Anesth.Analg. 1999; 88: 437-45
19. Ebert TJ, Arain SR: Renal responses to low-flow desflurane, sevoflurane, and propofol in patients. Anesthesiology 2000; 93: 1401-6
20. Ebert TJ, Messana LD, Uhrich TD, Staacke TS: Absence of renal and hepatic toxicity after four hours of 1.25 minimum alveolar anesthetic concentration sevoflurane anesthesia in volunteers. Anesth.Analg. 1998; 86: 662-7
21. Obata R, Bito H, Ohmura M, Moriwaki G, Ikeuchi Y, Katoh T, Sato S: The effects of prolonged low-flow sevoflurane anesthesia on renal and hepatic function. Anesth.Analg. 2000; 91: 1262-8

Chapter 7

Main conclusions and General discussion

Christiaan Keijzer, Roberto S.G.M. Perez, Jaap J. de Lange

Main conclusions

In this thesis we investigated the produced concentrations carbon monoxide (CO) and compound A (CA) as a result of interaction between inhalational anesthetics and carbon dioxide absorbents in hydrated and completely desiccated condition. To measure the maximum concentrations of CO and CA, comparable to a clinical situation, we created a patient model in which we connected an anesthesia machine to an artificial lung with a study protocol where vapor anesthetic and fresh gas flow were introduced, comparable with performance of anesthesia in clinical practice. To acquire the most accurate and reliable CO and CA measurements, we used a portable gas chromatograph with a high sensitivity TCD detector that automatically sampled from the anesthetic circuit every five minutes during the experiments. In the laboratory studies presented in **chapters 2-4** we used several carbon dioxide absorbents with different concentrations of strong bases.

In **chapter 2** we demonstrated the production of very high concentrations of CO in dry sodalime with desflurane and enflurane. The highest CO concentration is measured for desflurane, but when calculated per volume% of inhalational anesthetic, the concentration of CO is higher for enflurane. The CO production from isoflurane is less, but still significant. Contrary to previous reports, also sevoflurane and halothane can produce small amounts of CO. The average peak and mean concentration of CO measured in the experiments of **chapter 3** are displayed in table 7.1 for all tested absorbents, including the measurements from **chapter 2** regarding the measured CO concentrations from desflurane and Drägersorb 800 plus®.

Table 7.1: Peak and mean carbon monoxide concentration

CO_2 absorbent	Peak [CO]	Mean [CO]
Drägersorb 800 plus®	14075	3986
Medisorb®	13317	4562
Spherasorb®	9045	3395
LoFloSorb®	524	327
Superia®	31	14
Amsorb®	0	0
Lithium hydroxide	0	0

Concentrations in parts per million for each completely desiccated carbon dioxide absorbent used in combination with 3.0 vol% desflurane.

From these data we conclude that Drägersorb 800 plus® and Medisorb® generate the highest concentrations of CO, followed by Spherasorb®. These concentrations seem to be correlated to the concentration of NaOH inside the absorbent. The desiccated absorbent LoFloSorb® and Superia® produce only small amounts of CO and Amsorb® and lithium hydroxide do not generate any carbon monoxide.

In **chapter 4** areas under the curve are presented for CA and CO produced as a result of the interaction between 0.8 vol% sevoflurane and seven different absorbents in hydrated and desiccated condition. To demonstrate an overall picture of CA and CO concentrations produced in this study, we depicted the peak and mean concentrations for all experiments in **chapter 4** in table 7.2.

Table 7.2: Average measured peak and mean concentrations

CO_2 absorbent	Peak dry [CA] / [CO]	Peak fresh [CA] / [CO]	Mean dry [CA] / [CO]	Mean fresh [CA] / [CO]
Drägersorb 800 plus®	7.6 / 116.0	12.1 / 0.0	2.0 / 25.1	9.5 / 0.0
Medisorb®	5.4 / 31.1	7.4 / 0.0	1.8 / 8.1	6.9 / 0.0
Spherasorb®	6.2 / 40.6	2.2 / 0.0	1.8 / 10.4	1.7 / 0.0
LoFloSorb®	0.0 / 0.0	0.0 / 0.0	0.0 / 0.0	0.0 / 0.0
Superia®	0.0 / 0.0	0.0 / 0.0	0.0 / 0.0	0.0 / 0.0
Amsorb®	21.9 / 0.0	0.0 / 0.0	16.6 / 0.0	0.0 / 0.0
Lithium hydroxide	2.9 / 0.0	0.0 / 0.0	2.2 / 0.0	0.0 / 0.0

Concentrations in parts per million of compound A ([CA]) and carbon monoxide ([CO])for each absorbent in completely desiccated (dry) and hydrated (fresh) condition in combination with 0.8 vol% sevoflurane.

These data demonstrate that very low concentrations of CA are produced for Drägersorb 800 plus®, Medisorb®, Spherasorb® and desiccated Amsorb® and lithium hydroxide. LoFloSorb® and Superia® do not produce any concentration of CA under these circumstances. All absorbents with 2% or more NaOH demonstrated an decrease of measured CA when desiccated. Absorbents with less NaOH

produced more CA when desiccated. Absorbents free of NaOH, produced only CA when desiccated (Amsorb®, lithium hydroxide) or no CA at all (LoFloSorb®, Superia®). For all measured concentrations of CA we concluded that they are not clinically relevant, and will probably not cause nephrotoxicity.

In the studies in **chapter 2 and 4**, we could not establish any relationship between temperature and CA or CO production except for the experiments with desiccated Drägersorb®, Medisorb® and Spherasorb®. In these experiments we recorded a significant increase in temperature during the first 20 minutes of the experiments. In this time period, sevoflurane was extensively degraded but only small amounts of CO were produced (table 7.2).

In **chapter 5** we tested the reliability of an electrochemical carbon monoxide sensor compared to gaschromatography when carbon monoxide is produced as a result of interaction between halothane, enflurane, isoflurane, sevoflurane or desflurane and desiccated Drägersorb 800 plus®. From the data of this study we conclude that this electrochemical sensor is accurate within the specified range but displays a highly underestimated result when CO levels exceed this range. It could, however, provide an early warning sign of CO being produced in the initial stages of CO release.

The concentrations of CO measured in 40 patients presented in **chapter 6** demonstrates that no carbon monoxide is produced using desflurane or sevoflurane and sodalime. This is probably due to the fact that carbon dioxide absorbents need extensive dehydration before carbon monoxide can be produced. This is prevented in the VU University Medical Center due to the use of a safety protocol, whereby the fresh gas flow of the anesthesia machine is consistently closed after the operating program is finished. When a fresh gas flow is used to dry the ventilating circuits of the anesthesia machine, only a flow of air is used that contains a fraction of carbon dioxide and will therefore keep the absorbent hydrated. The CA concentrations found were somewhat higher than in the laboratory study because of the higher concentrations of sevoflurane used in this setup.

However the maximum measured concentration of CA was 37.5 parts per million, is too low to generate any detectable nephrotoxicity in humans[1;2].

General discussion

Limitations of the laboratory studies

In the presented patient model we did not add carbon dioxide to the artificial lung to simulate carbon dioxide production from the patient. We chose not to use carbon dioxide in this model because of its sparse effect on carbon monoxide production as published by Woehlck et al.[3]. Another well known limitation of every laboratory study investigating carbon monoxide production is the lack of carbon monoxide binding to hemoglobin. Carbon monoxide has a strong affinity for hemoglobin, and it is plausible that the binding of carbon monoxide to hemoglobin could have a significant effect on the measured carbon monoxide concentrations in the studies presented in **chapters 2-4**. To demonstrate this effect we compared our data from **chapter 1** with the data from an in vivo study by Frink et al.[4], where pigs were exposed to carbon monoxide production from partially desiccated Baralyme® or sodalime and desflurane. In figure 7.1 we depicted our results with the Baralyme® data from this in vivo study. This figure suggests that binding of carbon monoxide to hemoglobin leads to a more rapid decrease of measured CO concentrations (within 30 minutes, wheras 90 minutes were needed in our in vitro study). However, one should take into consideration that although CO concentrations are much lower after these 30 minutes in the in vivo study, the CO produced was bound to the hemoglobin of these pigs, therewith obtaining a lethal carboxyhemoglobin concentration of 72.6% after twenty minutes. Frink's in vivo study also demonstrated that lowering the water content of the absorbent increased the concentrations of CO produced. While a peak concentration of 13,600 ppm CO was measured in combination with Baralyme® containing 4.8% water, a concentration of 37,000 ppm was reported with Baralyme® with a water content of 1.2%. Wissing et al.[5] confirmed this concentration effect for five inhalational anesthetics and desiccated sodalime.

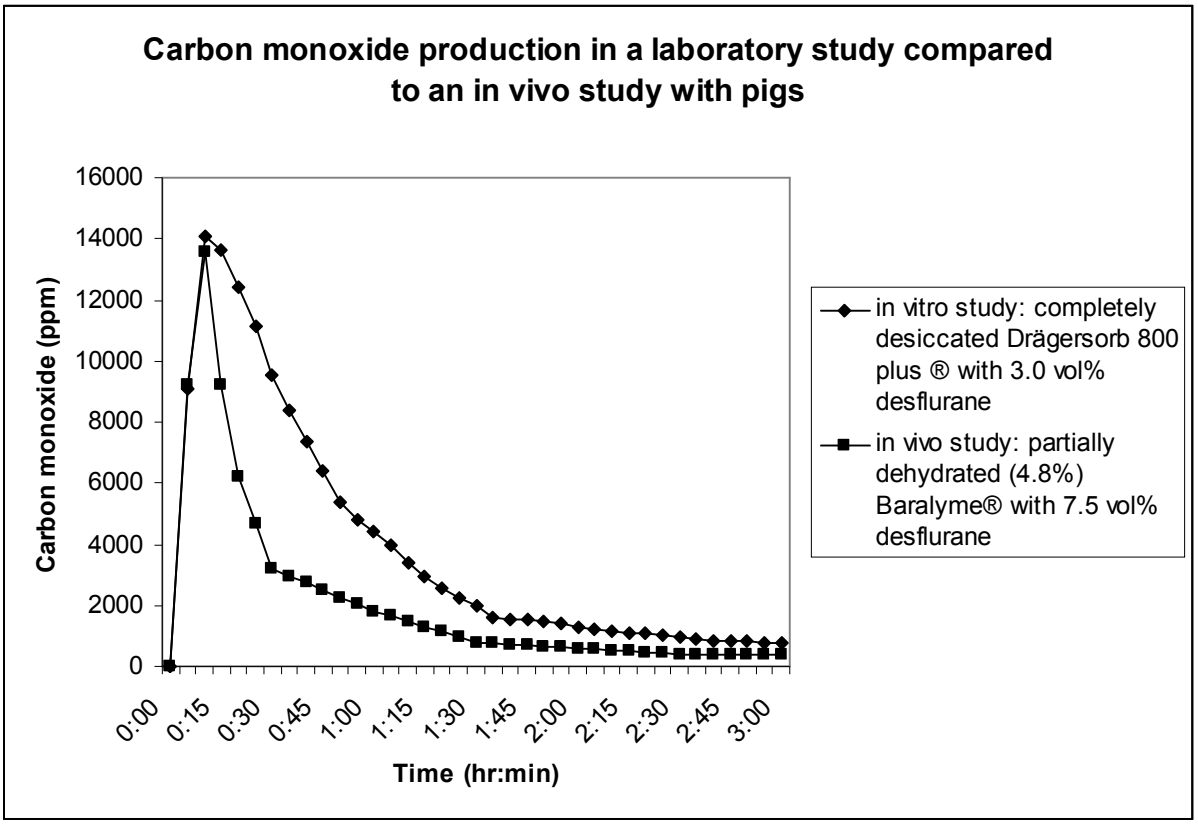


Figure 7.1 Carbon monoxide concentrations in parts per million (ppm) as a result of interaction between 3.0 vol% desflurane with completely desiccated Drägersorb 800 plus® (data from **chapter 2**) and 7.5 vol% desflurane with partially desiccated Baralyme®; **data used with permission from Lippincot Williams & Wilkins: Frink et al.: High carboxyhemoglobin concentrations occur in swine during desflurane anesthesia in the presence of partially dried carbon dioxide absorbents. Anesthesiology 1997; 87:308-16.**

In our laboratory studies we used approximately 1 MAC of anesthetic vapor in combination with 60% of nitrous oxide. Considering this concentration effect on carbon monoxide production, higher concentrations of CO are to be expected when using a higher concentration of volatile anesthetics without the use of nitrous oxide. For compound A production this concentration effect is also valid: higher concentrations of sevoflurane result in higher concentrations of CA as demonstrated in **chapter 6**.

Relationship between temperature and CO or CA production

Fang et al.[6] demonstrated that a higher temperature of the absorbent results in higher concentrations of CO. Two other studies[7;8] demonstrated the same effect for CA production. However, this temperature increase is not so much an indicator of CO production but of degradation of the

anesthetic inside the absorbent as demonstrated by Wissing et al.[5;9]. We can confirm these findings as indicated in the main conclusions section.

The extreme temperatures, fires and explosions published in several case reports[10-12] and two studies[13;14] are only described for sevoflurane in combination with the absorbent Baralyme®. The chemical composition of Baralyme® consists of 73% $Ca(OH)_2$, 11% $Ba(OH)_2$ and 4.6% KOH. It is probably this high concentration of the base KOH that is responsible for these high temperatures (more than 200°C have been reported), because other absorbents containing less KOH show sevoflurane degradation with less temperature increase. The maximum temperature increase with sevoflurane and the desiccated absorbents (free of KOH) in this thesis was 41.7°C. As a result of these recent case reports, Baralyme® was withdrawn from the American market. It was never used in Europe, and therefore not tested in our studies.

Detection of carbon monoxide inside the anesthetic circuit

Woehlck et al.[15;16] demonstrated that carbon monoxide can be recognized as enflurane by an infrared gas analyzer due to the trifluoromethane that is simultaneously formed. In our laboratory studies we used a Smart Anesthesia Multigas Module (SAM) from GE/Marquette Medical Systems during the experiments. In the experiments with desiccated Drägersorb 800 plus®, Medisorb® and Spherasorb® and 3.0 vol% desflurane, this SAM detected concentrations of enflurane that correlated with the measured carbon monoxide concentrations as described in **chapters 2 and 3**. This correlation varied between the absorbents and also the lower limit of detection was different for each absorbent. The enflurane detections disappeared for Drägersorb 800 plus® at a carbon monoxide concentration of 3422 parts per million (ppm), for Medisorb® at 1886 ppm and for Spherasorb® at 1526 ppm. To illustrate these differences, we depicted the measured CO concentrations by the GC against the measured enflurane concentrations by the SAM for these experiments in figures 7.2 to 7.4.

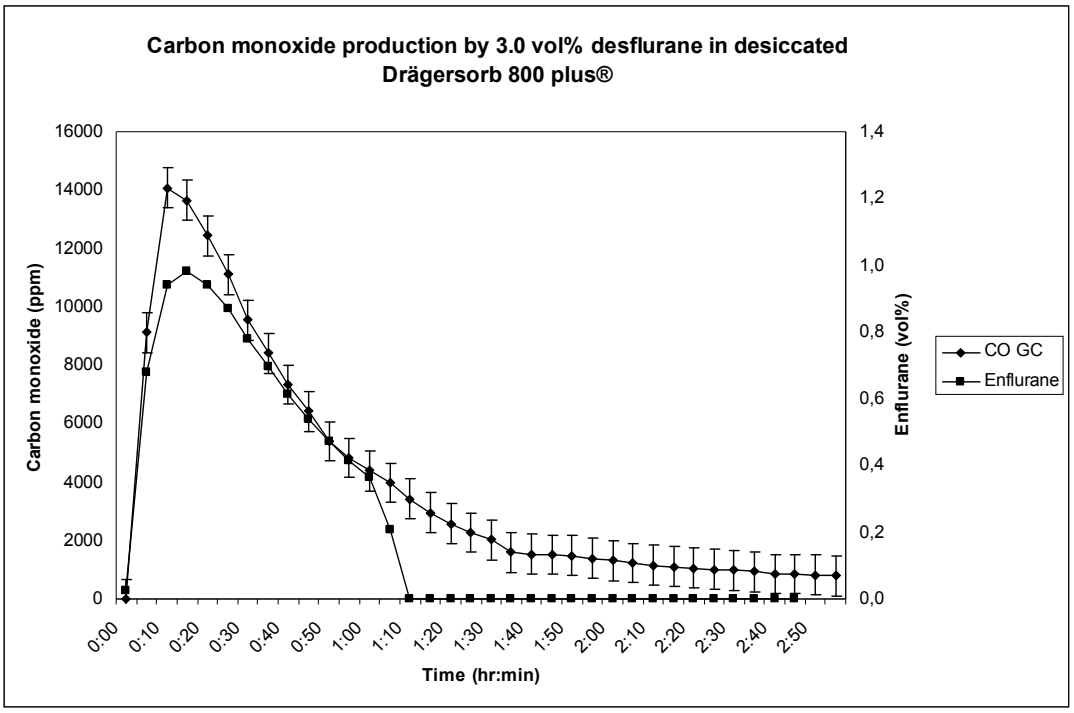


Figure 7.2 Carbon monoxide concentrations measured by the GC in parts per million (ppm) as a result of interaction between 3.0 vol% desflurane with completely desiccated Drägersorb 800 plus®. On the second Y-axis the measured concentration of enflurane is depicted in vol%. Correlation between the CO an enflurane concentrations is significant (Spearman's r : 0.80;$p<0.001$).

The production of trifluoromethane is not directly correlated with carbon monoxide production but depends on the type of anesthetic and absorbent used and duration time of the reaction[17]. This explains the different correlations and limits of detection of enflurane as a result of CO production. For example: in figure 7.2 the enflurane concentration line lies lower than the line of the carbon monoxide line, while in figures 7.3 and 7.4 these enflurane lines are higher and longer in duration. We therefore conclude that reported concentrations of enflurane from an infrared vapor analyzer indicate high concentrations of trifluoromethane and consequently high concentrations of carbon monoxide. From the figures 7.2 to 7.4 we conclude that there is agreement between carbon monoxide production and the concentration of trifluoromethane, but that this relationship is not linear. However this warning sign of enflurane detection already saved one life through adequate intervention by the anesthesiologist as reported by Berry et al.[18] (case report described in **chapter 1**).

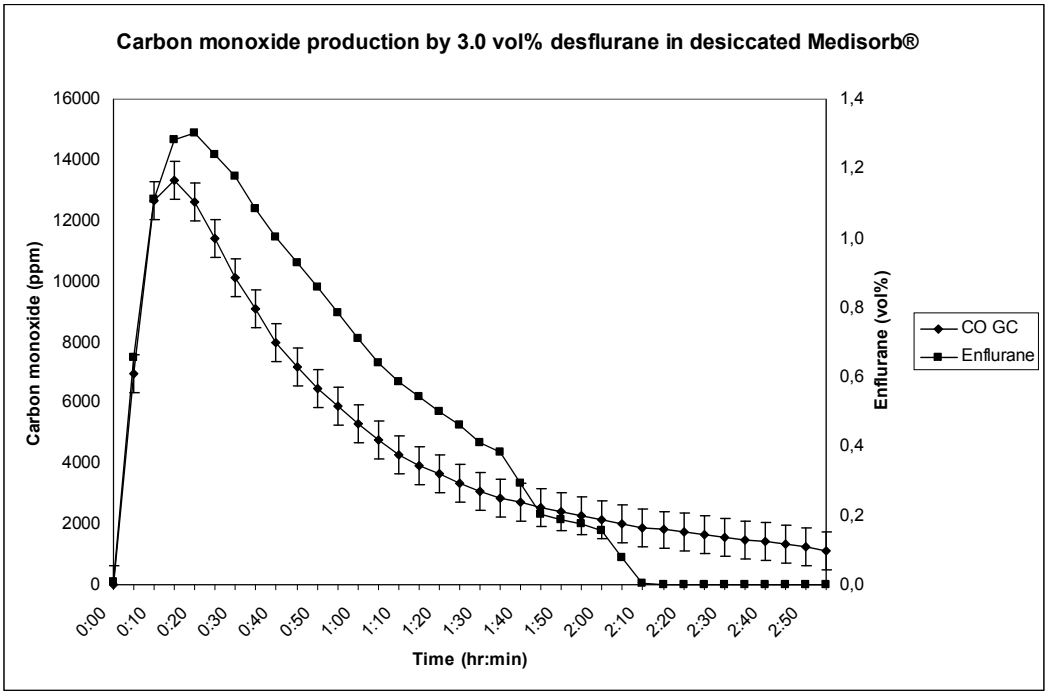


Figure 7.3 Carbon monoxide concentrations measured by the GC in parts per million (ppm) as a result of interaction between 3.0 vol% desflurane with completely desiccated Medisorb®. On the second Y-axis the measured concentration of enflurane is depicted in vol%. Correlation between the CO an enflurane concentrations is significant (Spearman's r : 0.98 ; $p<0.001$).

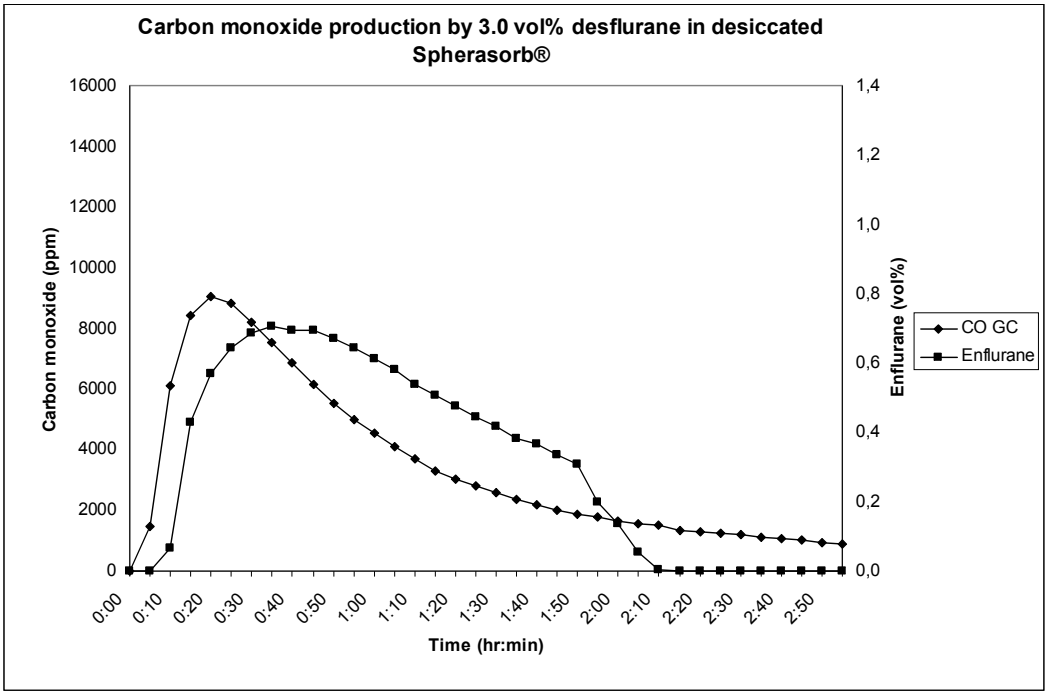


Figure 7.4 Carbon monoxide concentrations measured by the GC in parts per million (ppm) as a result of interaction between 3.0 vol% desflurane with completely desiccated Spherasorb®. On the second Y-axis the measured concentration of enflurane is depicted in vol%. Correlation between the CO an enflurane concentrations is significant (Spearman's r : 0.90;$p<0.001$).

Another method to detect carbon monoxide inside an anesthetic circuit is the use of an electrochemical CO sensor. The electrochemical sensor with a limited range of 0 – 200 ppm of CO tested in **chapter 5** is reliable within this range but displays an highly underestimated result with higher concentrations of CO. Other in vitro studies[19;20] demonstrated that electrochemical sensors with a larger range are also accurate within their specific ranges (0-500 and 0-1,999 ppm). Therefore it seems that the technique of electrochemical detection is accurate enough, but that sensors with much higher ranges have to be developed, to accurately detect the actual amounts at high concentrations of CO. For clinical practice, however, the warning provided by the electrochemical sensor is sufficient to prevent exposure of the patient to lethal CO concentrations.

Limitations of the in vivo study

The main limitation of the in vivo study presented in **chapter 6** is that it is an observational study, with a small number of patients. We hypothesized that the lack of carbon monoxide production is due to the implementation of a safety protocol but we did not test this. To demonstrate the effectiveness of this protocol it should be tested in a randomized trial, where a much larger number of patients would be anesthetized in either an operating theatre with or without this safety protocol. For ethical reasons this option was not considered.

Reference List

1. Eger EI, Gong D, Koblin DD, Bowland T, Ionescu P, Laster MJ, Weiskopf RB: Dose-related biochemical markers of renal injury after sevoflurane versus desflurane anesthesia in volunteers. Anesth.Analg. 1997; 85: 1154-63
2. Goldberg ME, Cantillo J, Gratz I, Deal E, Vekeman D, McDougall R, Afshar M, Zafeiridis A, Larijani G: Dose of compound A, not sevoflurane, determines changes in the biochemical markers of renal injury in healthy volunteers. Anesth.Analg. 1999; 88: 437-45
3. Woehlck HJ, Dunning M, III, Raza T, Ruiz F, Bolla B, Zink W: Physical factors affecting the production of carbon monoxide from anesthetic breakdown. Anesthesiology 2001; 94: 453-6
4. Frink EJ, Jr., Nogami WM, Morgan SE, Salmon RC: High carboxyhemoglobin concentrations occur in swine during desflurane anesthesia in the presence of partially dried carbon dioxide absorbents. Anesthesiology 1997; 87: 308-16
5. Wissing H, Kuhn I, Warnken U, Dudziak R: Carbon monoxide production from desflurane, enflurane, halothane, isoflurane, and sevoflurane with dry soda lime. Anesthesiology 2001; 95: 1205-12
6. Fang ZX, Eger EI, Laster MJ, Chortkoff BS, Kandel L, Ionescu P: Carbon monoxide production from degradation of desflurane, enflurane, isoflurane, halothane, and sevoflurane by soda lime and Baralyme. Anesth.Analg. 1995; 80: 1187-93
7. Morio M, Fujii K, Satoh N, Imai M, Kawakami U, Mizuno T, Kawai Y, Ogasawara Y, Tamura T, Negishi A, .: Reaction of sevoflurane and its degradation products with soda lime. Toxicity of the byproducts. Anesthesiology 1992; 77: 1155-64
8. Osawa M, Shinomura T: Compound A concentration is decreased by cooling anaesthetic circuit during low-flow sevoflurane anaesthesia. Can.J.Anaesth. 1998; 45: 1215-8
9. Wissing H, Kuhn I, Dudziak R: [Heat production from reaction of inhalation anesthetics with dry soda lime]. Anaesthesist 1997; 46: 1064-70
10. Fatheree RA, Leighton BL: Acute respiratory distress syndrome after an exothermic baralyme-sevoflurane reaction. Anesthesiology 2004; 101: 531-3
11. Castro BA, Freedman LA, Craig WL, Lynch III C: Explosion within an anesthesia machine: Baralyme, high fresh gas flows and sevoflurane concentration. Anesthesiology 2004; 101: 537-9
12. Wu J, Previte JP, Adler E, Myers T, Ball J, Gunter JB: Spontaneous ignition, explosion, and fire with sevoflurane and barium hydroxide lime. Anesthesiology 2004; 101: 534-7
13. Holak EJ, Mei DA, Dunning MB, III, Gundamraj R, Noseir R, Zhang L, Woehlck HJ: Carbon monoxide production from sevoflurane breakdown: modeling of exposures under clinical conditions. Anesth.Analg. 2003; 96: 757-64, table
14. Laster M, Roth P, Eger EI: Fires from the interaction of anesthetics with desiccated absorbent. Anesthesia and Analgesia 2004; 99: 769-74
15. Woehlck HJ, Dunning M, III, Gandhi S, Chang D, Milosavljevic D: Indirect detection of intraoperative carbon monoxide exposure by mass spectrometry during isoflurane anesthesia. Anesthesiology 1995; 83: 213-7
16. Woehlck HJ, Dunning MB, III, Kulier AH, Sasse FJ, Nithipataikom K, Henry DW: The response of anesthetic agent monitors to trifluoromethane warns of the presence of carbon monoxide from anesthetic breakdown. J.Clin.Monit. 1997; 13: 149-55
17. Woehlck HJ, Dunning M, III, Nithipataikom K: Monitoring of isoflurane and desflurane breakdown: interfering gases and infrared detection. J Clin Monit 2000; 16: 535-40
18. Berry PD, Sessler DI, Larson MD: Severe carbon monoxide poisoning during desflurane anesthesia. Anesthesiology 1999; 90: 613-6
19. Woehlck, H. J. and Dunning, M., III. Performance of a portable carbon monoxide monitor in the presence of inhalation anesthetics. Anesthesiology 85(3A), A429. 1996.
20. Bermudez JA: Investigation of electrochemical carbon monoxide sensor monitoring of anesthetic gas mixtures. Anesthesiology 2003; 99: 1233-5

Summary

Summary

Anesthesia is essential to facilitate most of the surgical procedures performed in hospitals. To make economical use of medical gases like oxygen and inhalational anesthetics, the anesthesiologist uses an anesthesia machine, that contains a circle ventilating circuit that allows rebreathing of expired gases from the patient. To facilitate this rebreathing of medical gases and volatile anesthetics, it is essential that exhaled carbon dioxide does not return to the patient. This is accomplished by using a carbon dioxide absorbent inside the circle ventilating circuit. There are several carbon dioxide absorbents, and they contain calcium hydroxide that binds carbon dioxide, and other chemicals that facilitate the binding of carbon dioxide to calcium hydroxide. Classic absorbents contain strong bases like potassium hydroxide (KOH) and sodium hydroxide (NaOH) as facilitating binding agents. These strong bases, however, are highly reactive and are to a large extent responsible for carbon monoxide (CO) production from inhalational anesthetics and carbon dioxide absorbents that have become desiccated. CO is a toxic gas, mostly produced as a result of incomplete combustion of organic materials. The average CO concentration in the atmosphere is 0.1 ppm (parts per million), but in cities with much traffic it can reach up to 115 ppm. Hemoglobin's affinity for carbon monoxide is 220 times that of oxygen, which can lead to hypoxia if CO concentrations are sufficiently high. A one hour exposure of 1500 ppm of CO is lethal for humans.

With the introduction of sevoflurane, it was soon demonstrated that from the interaction with carbon dioxide absorbents, a nephrotoxic degradation product was formed, named compound A (CA). CA is nephrotoxic in rats after a 3-hour exposure of 50 ppm, as established histologically. In humans however this concentrations does not generate any renal injury, and higher concentrations up to 240 ppm only demonstrates some transient nephrotoxicity in a few studies. CA is produced as a result of degradation of sevoflurane in desiccated as well as hydrated carbon dioxide absorbents. Absorbents without strong bases like KOH and NaOH, produce the lowest concentrations of CA.

In this thesis we investigated the CO production from all modern inhalational anesthetics and CA production from sevoflurane in combination with seven different types of carbon dioxide absorbents containing different concentrations of strong bases. The absorbents were tested in hydrated and completely desiccated condition. For the laboratory studies described in **chapters 2-5** we developed a patient model in which a standard anesthesia circle machine was connected to an artificial lung with a study protocol where volatile anesthetics and fresh gas flow were introduced in accordance with clinical practice. For accurate measurements of CO and CA a portable gas chromatograph was used.

In **chapter 1** we described the history of inhalational anesthetics and carbon dioxide absorption. Also, an overview of recent findings of the interactions between volatile anesthetics and carbon dioxide absorbents is presented. We measured the maximum concentrations of CO produced as a result of interaction between the five modern inhalational anesthetics (halothane, enflurane, isoflurane, sevoflurane and desflurane) and sodalime (i.e. Drägersorb 800 plus®) in hydrated and completely desiccated condition in **chapter 2**. Temperature was measured inside the absorbent, to investigate a possible relationship between temperature of the absorbent and carbon monoxide production. Very high concentrations of CO were measured with desflurane and enflurane, up to 14262 and 10654 parts per million (ppm) respectively. Lower but still toxic concentrations were found using isoflurane (2512 ppm), whereas non-lethal concentrations of CO were measured for sevoflurane (121 ppm) and halothane (210 ppm).

No CO was found with normally hydrated sodalime and no relationship could be established between temperature of the absorbent and the amount of CO production.

In **chapter 3** we investigated the amounts of CO produced as a result of interaction between desflurane and six different types of absorbent containing different concentrations of strong bases. This to establish the relationship between the strong base content of the absorbent and carbon monoxide production. Here we demonstrated that the desiccated absorbents with a relatively large

concentration of NaOH, namely Medisorb® and Spherasorb® produced high concentrations of CO. The absorbents free of strong bases produced small amounts of CO (Loflosorb® and Superia®) or no CO at all (Amsorb® and lithium hydroxide). None of the tested absorbents produced any CO when normally hydrated. Lithium hydroxide, however, is not yet available for medical use in anesthesia machines, because of it's highly corrosive effect. **Chapter 4** focuses on the interactions of sevoflurane and the seven different types of carbon dioxide absorbent described in **chapters 2 and 3**. We tested these absorbents in normally hydrated and desiccated condition and measured the temperature inside the absorbent, to investigate a possible relationship between CA and CO production and temperature inside the absorbent. We demonstrated that absorbents free of strong bases, Loflosorb®, Superia®, Amsorb® and lithium hydroxide do not produce any CA when normally hydrated, in contrast with absorbents containing strong bases. However, the absorbents Amsorb® and lithium hydroxide do produce small amounts of CA when desiccated. Small amounts of CO were produced by the desiccated strong base containing absorbents Drägersorb 800 plus®, Medisorb® and Spherasorb®, accompanied by sevoflurane degradation at the start of these experiments. No CO was produced with any of the absorbents in normally hydrated condition. No relationship between temperature and CA or CO production could be established. All measured concentrations of CA and CO do not appear to be clinically relevant.

Detection methods for the production of carbon monoxide inside an anesthetic ventilating circuit are not built in anaesthetic systems as a standard. We therefore investigated the reliability of an electrochemical CO sensor compared to the gold standard i.e. gas chromatography in **chapter 5**. In this study we found that the electrochemical sensor accurately detected carbon monoxide within the specified range of 0 – 200 ppm. Above this specified range this sensor underestimates the actual amounts of CO produced as measured by a gas chromatograph. However, this underestimated result still provides a warning signal of carbon monoxide production that requires immediate change of the carbon dioxide absorbent. When this sensor is exposed to sevoflurane in combination

with desiccated sodalime, it is not capable of normal operation and will display high and incorrect concentrations of CO within half an hour of operation.

In **chapter 6** we provide indications that carbon monoxide production in anesthetic practice is probably limited. In 40 patients receiving desflurane or sevoflurane anesthesia no CO production was found. This may be due to the effect of a safety protocol that was implemented in the VU University Medical Center with the introduction of desflurane. The purpose of this safety protocol is to prevent carbon dioxide absorbent desiccation. In all 20 sevoflurane anesthesia's, small concentrations of compound A were measured that where clinically insignificant.

In **chapter 7** the main conclusions and a general discussion of this thesis are presented.

Samenvatting

Chemische reacties tussen dampvormige anesthetica en kooldioxide absorbers

Koolmonoxide en compound A metingen in een anesthesie cirkelsysteem

Samenvatting

Anesthesie (ook wel narcose genoemd) is van wezenlijk belang om de meeste chirurgische ingrepen in ziekenhuizen te kunnen uitvoeren. Voor het toedienen van narcose zijn medische gassen zoals zuurstof en dampvormige anesthetica nodig. Om hier zuinig mee om te gaan maakt de anesthesioloog gebruik van een anesthesie machine met een cirkelvormig ventilatie circuit dat het mogelijk maakt dat uitgeademde lucht van de patiënt weer hergebruikt kan worden. Voordat deze uitgeademde lucht weer door de patiënt ingeademd kan worden, dient het koolstofdioxide (CO_2) gas daar eerst uit verwijderd te worden. Dit wordt gedaan door een zogenaamde CO_2-absorber, welke zich in het ventilatiecircuit bevindt. Er zijn verschillende soorten CO_2-absorbers op de markt, en deze bevatten naast calcium hydroxide ook andere chemische verbindingen om de reactie snelheid tussen het CO_2 en het calcium hydroxide te bevorderen. De klassieke CO_2-absorbers hebben daarvoor sterke basische verbindingen opgenomen zoals kalium hydroxide (KOH) en natrium hydroxide (NaOH). Deze basische verbindingen zijn sterk reactief en daardoor grotendeels verantwoordelijk voor de productie van koolmonoxide (CO) als reactieproduct van dampvormige anesthetica en uitgedroogde CO_2-absorbers. CO is een giftig gas, dat meestal geproduceerd wordt ten gevolgen van incomplete verbranding van organische materialen. De gemiddelde CO concentratie in de atmosfeer is 0,1 ppm (parts per million), maar kan in de grote steden oplopen tot 115 ppm. CO wordt 220 maal sterker gebonden aan het hemoglobine dan zuurstof, wat kan leiden tot een ernstig zuurstoftekort in het bloed als de CO concentratie hoog genoeg is. Een blootstelling van 1500 ppm gedurende één uur is dodelijk voor mensen.

Kort na de introductie van het dampvormig anestheticum sevofluraan bleek dat ook deze damp een reactie aanging met CO_2-absorbers, waarbij een afbraakproduct, genaamd compound A (CA), werd gemaakt dat schadelijk is voor de nier. CA veroorzaakt nierschade in ratten na een blootstelling van 50 ppm gedurende drie uur. Bij mensen echter, leidt deze blootstelling niet tot nierschade, zelfs

concentraties tot 240 ppm resulteerden niet in nierschade. Slechts enkele studies lieten een tijdelijke verhoging van gevoelige markers voor nierschade bij deze concentratie CA zien. CA is een afbraakproduct van sevoflurane en wordt geproduceerd door de interactie met zowel uitgedroogde als verse (water bevattende) CO_2-absorbers. Absorbers zonder de sterke basische verbindingen KOH en NaOH produceren de laagste concentraties CA.

In dit proefschrift onderzochten we de concentraties CO geproduceerd door alle moderne dampvormige anesthetica en CA productie door sevofluraan als gevolg van de interactie met zeven verschillende typen CO_2-absorbers, welke verschillende concentraties van de eerder genoemde sterk basische verbindingen bevatten. Deze CO_2-absorbers werden onderzocht als het normaal water bevattende (vochtige) absorber, en als volledig uitgedroogde absorber.
Voor de laboratorium studies in de **hoofdstukken 2-5** ontwikkelden we een patiëntmodel waarin een standaard type anesthesie machine met cirkelvormig ventilatiecircuit aangesloten werd aan een kunstlong. Tegelijkertijd werd gebruik gemaakt van een studie protocol waarin de toediening van dampvormige anesthetica en medische gassen conform de klinische praktijk werd uitgevoerd. Om CO en CA nauwkeurig te meten, werd gebruik gemaakt van een draagbare gaschromatograaf.

In **hoofdstuk 1** beschrijven we de geschiedenis van volatiele anesthetica en CO_2 absorptie. Tevens wordt een overzicht gegeven van de medische literatuur ten aanzien van de interactie tussen dampvormige anesthetica en CO_2-absorbers. In **hoofdstuk 2** hebben we de concentraties CO gemeten als gevolg van de chemische reactie tussen de vijf moderne dampvormige anesthetica (halothaan, enfluraan, isofluraan, sevofluraan en desfluraan) en de klassieke CO_2-absorber Drägersorb 800 plus®. Tegelijkertijd werd de temperatuur binnen in de absorber gemeten om te onderzoeken of er een mogelijk verband is tussen CO productie en temperatuur in de absorber.

In deze studie werden zeer hoge concentraties CO gevonden bij de droge absorber in combinatie met desfluraan en enfluraan, namelijk 14262 en 10654 parts per million (ppm). CO concentraties waren een stuk lager met isofluraan (2512 ppm) en zeer lage concentraties werden gemeten met sevofluraan (121 ppm) en halothaan (210 ppm). Er werd geen CO gemeten bij normaal vochtige absorbers en er kon geen relatie gevonden worden tussen temperatuur van de absorber en koolmonoxide productie.

In **hoofdstuk 3** hebben we onderzocht hoeveel CO er vrij komt door de chemische reactie tussen desfluraan en zes verschillende CO_2-absorbers met verschillende concentraties sterke basische verbindingen. Met dit onderzoek wilden wij de relatie tussen de hoeveelheid aanwezige basische verbindingen in de absorber en de hoeveelheid gemeten CO vaststellen. In deze studie toonden we aan dat de uitgedroogde absorbers met een hogere concentratie NaOH, zijnde Medisorb® en Spherasorb® een hoge concentratie CO produceerden. De absorbers die geen sterke basische verbindingen bevatten produceerden weinig (Loflosorb® en Superia®) tot geen CO (Amsorb® en lithium hydroxide). De vochtige absorbers produceerden geen van allen koolmonoxide. Ten aanzien van het mogelijk gebruik van lithium hydroxide als CO_2-absorber, moet opgemerkt worden dat dit product nog niet beschikbaar is voor gebruik in anesthesiemachines door de sterk etsende werking van het product. **Hoofdstuk 4** beschrijft een onderzoek waarin we gekeken hebben naar de reactie tussen sevofluraan en de zeven verschillende CO_2-absorbers zoals die beschreven zijn in de **hoofdstukken 2 en 3**. Ook hier zijn vochtige en volledig uitgedroogde absorbers getest en werd de temperatuur binnen in de absorber gemeten om te onderzoeken of er een relatie bestaat tussen CA en CO productie en de temperatuur in de absorber. In deze studie werd aangetoond dat de absorbers die geen sterke basische verbindingen bevatten, namelijk Loflosorb®, Superia®, Amsorb® en lithium hydroxide, geen CA produceerden als zij vochtig waren. Dit in tegenstelling tot de absorbers die wel basische verbindingen hadden. Tegelijkertijd moet opgemerkt worden dat de absorbers Amsorb® en lithiumhydroxide® wel CA produceerden als zij volledig uitgedroogd waren. Slechts

kleine hoeveelheden CO kwamen vrij bij de uitgedroogde absorbers Drägersorb 800 plus®, Medisorb® en Spherasorb®, welke allen sterk basische verbindingen bevatten. Aan het begin van deze experimenten bemerkten wij tevens een duidelijke afbraak van sevofluraan in het ventilatie circuit. Alle vochtige absorbers lieten geen CO productie zien en er kon geen relatie vastgesteld worden tussen de temperatuur van de absorber en CA of CO productie. Alle gemeten concentraties CA en CO waren zo laag dat zij niet klinisch relevant lijken te zijn.

Koolmonoxide wordt niet standaard gemeten in een anesthesie ventilatie circuit. Daarom hebben wij in **hoofdstuk 5** gekeken naar de betrouwbaarheid van een elektrochemische CO sensor in vergelijking tot de gouden standaard, gas chromatografie. In dit onderzoek zagen we dat de elektrochemische sensor accuraat CO detecteerde binnen het opgeven bereik van de sensor (0 – 200 ppm). Daarboven werden lagere waarden gemeten dan die gemeten door de gaschromatograaf. Tegelijkertijd gaven deze onderschatte waarden wel een alarmsignaal af dat CO op dat moment geproduceerd werd en men dus de kennelijk uitgedroogde absorber moest verwisselen door vochtige. In een experiment met sevofluraan en droge absorber bleek deze sensor niet goed te functioneren en werden veel te hoge waarden aangegeven binnen het eerste half uur van het experiment.

In **hoofdstuk 6** tonen we aan dat CO productie in de klinisch anesthesiologische praktijk waarschijnlijk niet vaak voorkomt. Bij 40 patiënten die een anesthesie ondergingen met behulp van desfluraan of sevofluraan werd geen koolmonoxide gemeten. Dit is mogelijk door de implementatie van een veiligheidsprotocol in het VUMC dat uitdroging van CO_2-absorbers moet voorkomen. Dit protocol werd tegelijkertijd gestart met de introductie van desfluraan. Bij alle 20 patiënten die een anesthesie met sevofluraan ondergingen, werden kleine hoeveelheden compound A gemeten die klinisch niet relevant lijken te zijn. In **hoofdstuk 7** worden de belangrijkste conclusies samengevat en een discussie over de bevindingen weergegeven.

Publications

Papers

Keijzer C, Perez RS, de Lange JJ. Detection of carbon monoxide production as a result of the interaction of five volatile anesthetics and desiccated sodalime with an electrochemical carbon monoxide sensor in an anesthetic circuit compared to gas chromatography. J Clin Monit Comput. 2007 Aug; 21: 257-64

Huitink JM, Balm F, Keijzer C, Buitelaar DR. Awake fibrecapnic intubation in head and neck cancer patients with a difficult airway: new findings and refinements to the technique. Anaesthesia 2007 Mar; 62: 214-219

Keijzer C, Perez RS, De Lange JJ. Compound A and carbon monoxide production from sevoflurane and seven different types of carbon dioxide absorbent in a patient model. Acta Anaesthesiol Scand. 2007 Jan; 51: 31-37

Keijzer C, Perez RS, de Lange JJ. Carbon monoxide production from desflurane and six types of carbon dioxide absorbents in a patient model. Acta Anaesthesiol Scand. 2005 Jul;49(6):815-8

Keijzer C, Perez RS, de Lange JJ. Carbon monoxide production from five volatile anesthetics in dry sodalime in a patient model: halothane and sevoflurane do produce carbon monoxide; temperature is a poor predictor of carbon monoxide production. BMC Anesthesiol. 2005 Jun 2;5(1):6

Perez RS, Keijzer C, Bezemer PD, Zuurmond WW, de Lange JJ. Predictive value of symptom level measurements for complex regional pain syndrome type I. Eur J Pain. 2005 Feb;9(1):49-56

Keijzer C, Perez RS, de Lange JJ. Carbon monoxide and Compound A measurements with desflurane and sevoflurane anesthesia in humans: an observational study. *Submitted for publication*

Abstracts

Johannes M Huitink, Christiaan Keijzer, Dirk R Buitelaar. Awake Fibrecapnic Intubation in Head and Neck Cancer Patients with a Difficult Airway: A Single Centre Case Series.
Abstractbook Difficult Airway Society Meeting, page 104, Octobre 4-6th 2006 Dublin ,Ireland

Keijzer C, Perez RS, De Lange JJ. Compound A production from sevoflurane and seven types of carbon dioxide absorbents in a patient model. Eur J Anesth 2006;23 (suppl 37): A-958

Keijzer C, Perez RS, De Lange JJ. Detection of carbon monoxide by an electrochemical carbon monoxide sensor in an anaesthetic circuit. Anesthesiologendagen 2006: P27

Engelbrecht WJ, Keijzer C, Boer C, de Lange JJ. Sevofluraan in bufferoplossingen: meten is weten. Ned Tijdschr Anesthesiol 2005; 18:P39

Perez RS, Keijzer C, Zuurmond WWA, De Lange JJ. Relationship between severity of impairment and health related quality of life in CRPS I. Eur J Anesth 2004; 21 (suppl 23): A796

Keijzer C. Perez RS, De Lange JJ. Carbon monoxide production from five volatile anesthetics in dry sodalime in a patient model: halothane and sevoflurane do produce carbon monoxide. Eur J Anesth 2004; 21 (suppl 23): A841

Bauer MJM, Perez RS, Keijzer C, Zuurmond WWA, De Lange JJ, Who cares after daycare. Ned Tijdschr Anesth 2004; 17 (suppl): 17

Keijzer C, Perez RS, de Lange JJ. Koolmonoxide & compound A-productie door verschillende CO2-absorbers. Ned Tijdschr Anesthesiol 2002;15:P 29

Other publications:

Huitink JM, Balm F, Keijzer C, Buitelaar DR,. Awake fibrecapnic intubation – A reply. Anaesthesia 2007 Jul; 62: 746

Keijzer C, de Lange JJ. Anesthesiologie, tweede druk 2007, hoofdstuk 2: Monitoring

De Lange JJ, Keijzer C. Anesthesiologie, tweede druk 2007, hoofdstuk 5: Inhalatieanesthetica

Keijzer C. Bekwaam, maar nog niet bevoegd. Medisch Contact 2006; 47: 1909

Keijzer C, Zuurmond WWA. Pijnbehandeling vraagt om een individueel zorgplan. Pijnperiodiek 2005; 3:2-3

Dankwoord

Eindelijk is daar dan het moment gekomen: een voltooid en goedgekeurd proefschrift en een vastgestelde promotiedatum. Een promotietraject dat begon in 2000 gedurende mijn opleiding tot anesthesioloog in het VU medisch centrum en waar vele uren vrije tijd in zijn gaan zitten. Een ieder die dit leest zal zich dan ook kunnen voorstellen hoe gelukkig ik ben met dit voltooide proefschrift. Uiteraard heb ik het allemaal niet in mijn eentje gedaan en daarom wil ik dan ook alle mensen bedanken die een bijdrage hebben geleverd aan mijn onderzoek en/of dit proefschrift, waarbij ik een aantal mensen met name willen noemen:

Allereerst natuurlijk mijn promotor, prof.dr. J.J. de Lange: beste Jaap, ik wil je bedanken voor al je inspirerende ideeën en begeleiding tijdens mijn wetenschappelijke stage in 1997 en gedurende het promotieonderzoek dat voortkwam uit de verrassende resultaten van deze wetenschappelijke stage. Vooral ook dank voor al jouw aanmoedigingen en support welke mij scherp hielden en inspireerden om de tijd te vinden om tot publicaties te komen. Dank ook voor jouw inspanningen als mijn opleider anesthesiologie en de mogelijkheden die je mij al tijdens mijn opleiding gaf om tijd te kunnen besteden aan het opleiden van collega's tot anesthesioloog in het VUMC.

Een proefschrift is nergens zonder gepubliceerde hoofdstukken en op het moment dat ik dit schrijf, zijn er inmiddels vier gepubliceerd. Zeer grote dank hiervoor ben ik verschuldigd aan mijn copromotor, dr. R.S.G.M. Perez. Beste Roberto, ik ben je reuze dankbaar voor alle tijd die je hebt besteed aan mijn artikelen voordat we ze instuurden, je hebt me enorm geholpen met het soms frustrerende reviewproces van tijdschriften waarbij ik me inmiddels realiseer dat het ik het nog vrij makkelijk heb doorlopen.

De aanleiding voor dit promotieonderzoek waren de resultaten van een wetenschappelijke stage welke ik in 1997 in het VUMC mocht doen. Het onderwerp voor dit drie maanden durende onderzoek werd aangebracht door dr.ir. Henk Ros, de klinisch fysicus van de afdeling anesthesiologie toentertijd, naar aanleiding van een aantal verschenen casuïstische mededelingen over koolmonoxide productie in anesthesiesystemen. Henk bracht mij ook in contact met dr.ir. Huib van Genderingen, klinisch fysicus van de afdeling fysica en medische techniek van het VUMC. Huib heeft mij in die tijd intensief begeleid met het opzetten van een meetmethode met behulp van een elektrochemische koolmonoxidesensor gekoppeld aan een anesthesietoestel en de uiteindelijke uitvoering van de experimenten met desfluraan en sevofluraan. Beste Henk, beste Huib, helaas zijn jullie mij en de afdeling anesthesiologie van het VUMC veel te vroeg ontvallen maar ik gedenk jullie met eerbied voor de tijd die jullie in mij geïnvesteerd hebben om mij in te wijden in de voor mij toen nog magische wereld van meetmethoden, fysica, calibratie van meetmethoden, digitaal/analoog conversies en vele andere onderwerpen. Ik hoop dat het jullie goed gaat in een andere en betere wereld.

Een aantal andere mensen hebben ook een grote technische bijdrage geleverd aan mijn promotieonderzoek en meetopstelling: ing. Nico van Schagen en Bert Hoogerheijde, dank voor al jullie inspanningen om mij van de juiste materialen en meetapparatuur te voorzien. Piet de Goede en dr. Daan Touw van het laboratorium van de apotheek in het VUMC voor jullie hulp bij de aanschaf van de juiste gaschromatograaf en jullie uitleg over meetmethoden bij gaschromatografie.

Het doen van laboratoriumexperimenten is leuk als je resultaten ziet ontstaan maar gedurende elk drie uur durend experiment waren er toch ook regelmatig momenten waarbij het gevoel ontstond dat ik naar groeiend gras aan het kijken was. Ik wil dan ook alle assistenten anesthesiologie bedanken die mij regelmatig kwamen opzoeken in mijn 'laboratorium' op het OK complex voor een praatje waardoor ik niet helemaal afgleed tot een 'kluizenaars nivo'. Beste Edward, Hans, Jan, Marc, Marcel, Martijn, Michael, Sjoerd en vele anderen, bedankt voor jullie gezelschap, aandacht en belangstelling.

Ik wil ook alle andere mensen uit het VUMC bedanken waar ik mee heb samengewerkt tijdens en na mijn opleiding tot anesthesioloog. Dank voor de leuke tijd die ik in het VUMC heb gehad.
Dank ook aan de dames van het secretariaat anesthesiologie van het VUMC voor hun hulp bij de vele administratieve zaken rondom dit proefschrift, dank ook voor jullie altijd warme belangstelling. Prof.dr. Wouter Zuurmond wil ik bedanken voor zijn 'aanmoedigingen' om te promoveren, als mij stellingen waren toegestaan had ik graag één van zijn vele citaten willen gebruiken: "bij het voorschrijven van sedatie dient de dokter bij kennis te zijn". Dr. Arthur Bouwman wil ik bedanken voor het mogen gebruiken van de lay-out van zijn proefschrift dat model heeft gestaan voor de lay-out van mijn proefschrift. Kaj Gigengack wil ik bedanken voor zijn inspanningen om tijd vrij te maken voor mijn onderzoek in het VUMC, maar vooral ook wil ik hem danken voor zijn vriendschap. Beste Kaj, we spreken elkaar gelukkig nog regelmatig ondanks het feit dat wij beiden nu in andere ziekenhuizen werken, ik weet dan ook zeker dat onze vriendschap een blijvende is.

Het schrijven van artikelen kost veel tijd, tijd die vaak gevonden wordt in de avond- en weekenduren, het voltooien van een compleet proefschrift is toch wel een ander verhaal. Ook dit heeft vele vrije uren gekost maar echt tempo heb ik pas kunnen maken toen ik inmiddels een klein jaar aan het werk was in het Nederlands Kanker Instituut – Antoni van Leeuwenhoek Ziekenhuis als anesthesioloog op de afdeling anesthesiologie en intensive care. Deze afdeling heeft mij ruim twee maanden schrijftijd gegeven waardoor ik in hoog tempo mijn laatste hoofdstukken van het proefschrift kon schrijven. Ik ben het NKI-AVL dan ook zeer erkentelijk voor het faciliteren van de voltooiing van dit proefschrift, een onderzoeksinstituut meer dan waardig. Veel dank ook aan mijn collega anesthesiologen in het NKI-AVL: beste Dick Buitelaar, Julia ten Cate, Tina Efthymiou, dr. Hans Huitink, May Ronday, Peter Schutte, dr. Michael Srámek en dr.med. Tino Stoppa, dank voor jullie warme belangstelling voor mijn wetenschappelijke activiteiten en het beschikbaar stellen van mijn 'schrijftijd'. Dank ook aan deze collega's en alle mensen op het OK complex en intensive care van het NKI-AVL voor de geweldige werkomgeving die jullie met z'n allen neerzetten en mij ontzettend veel inspiratie, werkplezier en energie opleveren!

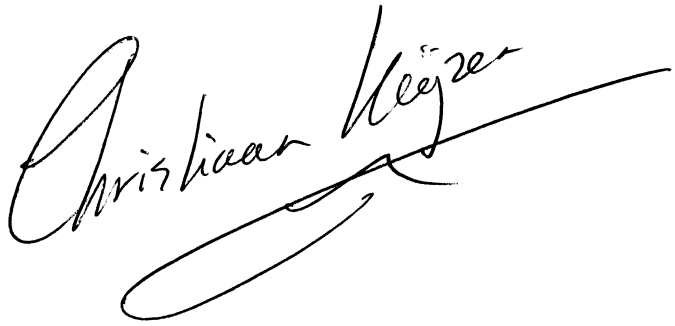
Bij deze wil ik ook de leden van de leescommissie bedanken voor het beoordelen van mijn proefschrift. Prof.dr. M.A. Blankenstein, prof.dr. A.R.J. Girbes, prof.dr. C.J. Kalkman, prof.dr. J. Klein, dr. J.G.C. Lerou en prof.dr. S.A. Loer, dank voor uw tijd om dit proefschrift te beoordelen en uw bijdrage als opponenten tijdens mijn openbare verdediging.

Dank aan mijn paranimfen en beste vrienden: Jeroen Manders en Ron Hameleers, dank voor jullie belangstelling en warme vriendschap. Ik hoop dat we elkaar nog lang mogen lastig vallen met onze vreugdevolle en minder vreugdevolle periodes in ons leven. Dank ook aan andere vrienden die altijd belangstellend waren naar dit onderzoek en mijn leven, bedankt Aletta v/d Stelt, Marjolein v/d Pol, Jeroen de Jong en Jeroen Nieuwenhuis.

Bedankt lieve Pa en Ma, voor jullie ondersteuning gedurende mijn hele leven waardoor ik uiteindelijk zover ben gekomen. Ik koester alle tijd die wij samen met Angelique, Casper en Mathijs doorbrengen en ik hoop dan ook dat we nog vele jaren veel tijd aan elkaar zullen blijven besteden.

Dank ook aan mijn schoonfamilie: lieve Lisette, Wijnand, Mireille, Theo, Roan, Iona, Dennis en Eef, dank voor jullie support en aandacht. Jullie zijn een bijzondere liefdevolle familie waar ik mij thuis in voel.

Als laatste het belangrijkste in mijn leven, mijn lieve vrouw en kinderen. Lieve Casper en Mathijs, dank voor jullie liefde en begrip als papa weer eens achter de computer moest in plaats van buiten met jullie spelen. Allerliefste Angelique, van jou weet ik 100% zeker dat jij alle stukken uit dit proefschrift in meerdere versies hebt gelezen, dank voor al jouw correcties op spel- en grammaticale fouten en jouw toetsing op de begrijpelijkheid van alle stukken voor de niet-anesthesiologische lezer. Dank ook voor jouw steun, begrip en aanmoedigingen om dit proefschrift te voltooien. Je bent en blijft de liefde van mijn leven!



About the author

Christiaan Keijzer was born on May 8th 1969 in Zutphen. From 1981-1987 he followed his undergraduate education at the Baudartius College in Zutphen. He subsequently started his medical education at the Radboud University in Nijmegen and graduated in 1997. During medical education he investigated the carbon monoxide production from desflurane and sevoflurane with dessicated Drägersorb® at the department of anesthesiology of the VU University Medical Center, under the supervision of prof.dr. J.J. de Lange and dr.ir. H.R. van Genderingen. For carbon monoxide quantification an electrochemical sensor was used. After an internship at the intensive care unit of the Medical Center 'De Klokkenberg' in Breda (now the Thoracic Center of the Amphia hospital in Breda) he followed his anesthesiology resident training at the department of anesthesiology of the VU University Medical Center in Amsterdam from 1999 until 2004 under the supervision of prof. dr. J.J. de Lange. During anesthesiology residency he performed the laboratory studies described in this thesis. From 2004 until 2006 he worked as an anesthesiologist in the VU University Medical Center, where he conducted the human study described in this thesis. Currently he is working in the Netherlands Cancer Institute – Antoni van Leeuwenhoek Hospital in Amsterdam, where he concluded this thesis.

Christiaan Keijzer is married to Angelique Keijzer-Broeders and they have two sons, Casper (2001) and Mathijs (2003).